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FOREWORD

In view of the fact that cancer is holding the center of the American medical stage to-day, it seems fitting that our Journal, RADIOLOGY, should appear in a special edition limited to the subject *cancer*. The Radiological Society of North America, realizing the importance of this study, has featured a Cancer Symposium at each of its annual meetings, and this present issue contains, therefore, the papers on this subject which were presented before this Society at the Toronto meeting just concluded. The writer feels that, inasmuch as the contents of this issue represent broadly scientific facts pertaining to the incidence, pathology, diagnosis, and treatment of cancer, the cancer student may find within its pages sufficient material of interest to warrant its careful perusal.

It must be admitted that research into the science of radiology has been instrumental in bringing the cancer problem up to its present point of activation. Then, who can deny the possibility that by these selfsame endeavors the whole mysterious cancer problem may be solved through this very research, which is being so splendidly supported by the type of men who contribute these papers?

The officers of the Radiological Society of North America, who have authorized the publication of this special issue, and the Editor of RADIOLOGY, sincerely trust that all the members of the Society and the subscribers to the Journal will appreciate the effort made in the preparation of this issue and will approve of its contents.

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Chairman, Cancer Symposium.

FACTORS DETERMINING RADIORESISTANCE IN TUMORS[1]

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THE factors determining radioresistance in tumors are very numerous. They consist mainly in structural components of the tumor but arise as the result of many complicating conditions that occur in the course of tumor growth. A general conception of the subject may perhaps best be obtained by a review of various tumors and an inquiry into the nature of the resistance in each. Consideration of what may be accomplished by radiation in each of these groups may also be attempted.

(1) *Resistance due to adult character of stroma.*—This form of resistance is observed in many types of sarcoma, osteogenic, neurogenic, chondrosarcoma.

The stroma of many osteogenic sarcomas consists of bone, osteoid tissue, hyaline material, fibrous tissue, and often cartilage. All of these structures resist radiation and cannot be absorbed. There is a very great variety of such tumors so that the exact fate of any one of them under radiation is difficult to predict, but in general they do not diminish in size under treatment. Their nutrition, however, is much affected, and pronounced regressive changes may be produced with the deposit of calcific material, liquefaction with cyst formation, and hyaline fibrosis. The attempt to secure extreme regression generally leads to painful radiation osteitis and spontaneous fracture. The best results seem to be obtained by repeated, full, but not excessive doses, aiming at growth restraint. That such efforts may be worth while seems to be shown by the following cases.

Case 1. *Osteogenic sarcoma of lower end of femur in a girl 18 years of age.*—Devitalization of a cellular bone tumor without reduction in size. Thirteen X-ray treatments, high voltage, over a period of two years. Spontaneous fracture. Amputation two and one-half years after onset. No metastases. Well eight years.

Examination of the tumor revealed that the growth, 12 x 14 cm. in diameter, had been liquefied in the central portions, while a thick shell of osteoid and fibrous tissue remained. Sections showed stainable tumor cells, without evidence of growth activity. The tumor had been largely devitalized, without reduction in size. The fact that no metastases had occurred in two and one-half years, we are inclined to refer to the effects of radiation. We now have records of several similar cases in which the usual metastases of osteogenic sarcoma failed to occur after radiation, although the limb had to be amputated.

Case 2. *Medullary fibrosarcoma of femur in a female subject, 33 years old.*—Cessation of growth after prolonged radiation. Fibrous union. Amputation after three years.

Examination of the tumor revealed a very firm mass of fibrous tumor tissues replacing the lower four inches of the femoral shaft. The structure of the original tumor showed a highly resistant fibrosarcoma, with much fibrous stroma and large spindle tumor cells. In the amputated tumor the cells were very scanty, and the stroma hyaline. The tumor had been devitalized. The patient has been well for eight years. The absence of metastases was to be expected from the fibrous character of the tumor. The radiation therefore accomplished nothing of value to this patient.

Chondromas and chondrosarcomas are resistant to radiation, but growth may be restrained, central softening may occur, and local extensions and metastases may be prevented.

Case 3. *Bulky chondroma of the os calcis in a boy 4 years old.*—Persistent radiation caused cessation of growth and progressive calcification of the tumor. At

[1]Read before the Radiological Society of North America at the Fifteenth Annual Meeting, at Toronto, Dec. 2-6, 1929.

the end of four years the tumor was slightly reduced in size, but the natural growth of the foot made the disproportion in size between heel and foot so slight that the child now has normal use of the latter.

Neurofibromas and the more cellular tumors verging toward neurosarcoma are generally quite resistant because of their dense stroma. Yet, in many instances persistant radiation with moderate doses may restrain growth and prevent the natural evolution of the tumor. There are two advantages in the radiation treatment of resistant neurofibromas: First, many of the tumors recur after operation, and in more cellular aggressive form; second, many of the tumors of the subcutaneous nerves are multiple, and the multiple tumors arise at successive periods, so that operation is often followed by the development of a new tumor in the same nerve trunk. Radiation, extending over a wide area of the affected nerve trunk, tends to prevent the appearance of new tumors. As neurofibromas become more cellular and therefore more malignant and more certain to recur after operation, they become less radioresistant. Hence, the effort to control them by carefully planned radiation is desirable and often successful.

As an exception to the rule that highly fibrous adult tumors are resistant, we have the example of the keloid, which responds slowly to full dosage, probably because the nutrition is dependent upon many fine lymph spaces which are obliterated by radiation.

(2) *The adult characters of epithelial cells and the substantial blood supply render adenomas and papillomas radioresistant.* Adenomas of breast and thyroid gland, and papillomas of skin, mucous membranes, and larynx, fail to respond, as a rule, to rather full dosage. I do not find a report of any systematic effort to determine what may be accomplished by small repeated doses and a long period of observation in the treatment of such tumors. Papillomas of the bladder generally require interstitial radiation of the pedicle, which cuts off the blood supply.

As an exception to the rule with adult tumors, myoma uteri responds to radiation, with widespread liquefaction and absorption of the relatively adult muscle cells. Here again, it seems probable that interference with blood supply plays an important part.

(3) *Carcinomas are resistant in inverse proportion to the degree of anaplasia and in direct proportion to the amount of desmaplastic reaction which they excite.* Many carcinomas are really disseminating infiltrating adenomas in which the anaplasia is only slightly greater than in adenomas. This group includes adenoma malignum and many alveolar carcinomas. As the anaplasia increases, the resistance diminishes. There are so many and such wide differences in the degree of anaplasia of carcinomas, that the attempt to grade them according to radiosensitivity is justified. Indeed, this investigation often succeeds in explaining the variable results of radiation and serves as a valuable guide in the plan of treatment. I believe that with increasing experience the grading of tumors from this standpoint will become much more accurate and reliable than it is at present possible to make it, and I have little sympathy with those who would dismiss the subject as impracticable. Such studies call for a very careful analysis of the structure, nutrition, and physiology of tumors, all of which themes lead to increased knowledge of the nature of the diseases with which we have to deal.

(4) *In mixed tumors in which one element is sensitive and the other resistant, the malignant portion may be sterilized, although the tumor does not diminish in size and a false impression of radioresistance may be gained.* This situation arises with mixed embryonal and adult tumors of the testis. The embryonal carcinomatous ele-

ments are sensitive and usually yield to moderate dosage, but the adult areas of cartilage, fibromuscular tissue, gland remnants, and epithelial cysts do not shrink, and the tumor remains unaltered in size, although deprived of its growth capacity. Comparative radioresistance is also observed with many adenocarcinomas of the testis. An occasional source of spurious resistance arises when hemorrhage occurs in a very vascular tumor, converting it into a hematoma. This event was demonstrated in a recent case of very vascular carcinoma of the testis.

Many other teratomatous tumors in other situations, as abdomen, kidney, and sacral region, exhibit the same complex structure and the same spurious resistance to radiation.

(5) *A special case of spurious resistance is observed, with very vascular giant-cell tumors, which are well designated as benign bone aneurysms.*

Case 4. Female, 35 years of age. Presented a multicystic tumor of the lower end of the femur which was diagnosed as a giant-cell tumor. Radiation treatment was instituted with the usual moderate doses, but the tumor continued to increase in size quite rapidly so that the suspicion of a malignant character was gained. After reaching very large dimensions, the limb was amputated. Examination revealed a large multicystic tumor with free arterial connections, the cysts being filled with blood. Sections showed that the tumor tissue had been largely devitalized, but the weakened capsule was unable to withstand the intermittent pressure of the blood stream and extensive dilatation occurred in a devitalized benign tumor. Other cases of the same type have been observed.

(6) *The nature of the tumor bed has much influence on the response to radiation, both favoring and in other cases retarding the response to treatment.* The high resistance of malignant tumors invading bone or cartilage is well known. In fat tissue also carcinomatous cell groups generally resist radiation and require caustic doses for control. I believe that this influence of fat tissue is one of the main reasons why mammary cancer shows such high relative radioresistance. The fat tissue does not permit easy access of blood, leukocytes, and plasma cells, and granulation tissue will not develop in it unless there has been necrosis of fat, and this requires caustic doses. These observations are difficult of explanation by those who hold that the regression of tumors is due solely to the destructive effect of the rays upon the tumor cells.

(7) *It is well known that infected tumors which are the seat of exudative inflammation do not react well to treatment, but a full explanation of this fact is difficult to find.* About foci of polynuclear leukocytes in infected tumors I sometimes find very numerous mitoses. It is said that leukocytes furnish growth-stimulating substances to tumor cells in culture. The infection loosens the surrounding tissues and permits infiltration by invading tumor cells, which more readily penetrate tissue spaces, vessels, and lymphatics. Radiation also tends to accelerate the inflammatory process. Yet the high circulation and metabolism of infected tumors should render them more sensitive to radiation. The poor results of treating infected tumors indicate that a suitable environment of the tumor is an essential factor in bringing about regression.

(8) *Acquired resistance.*—The increased resistance acquired by tumor cells which have been subjected to repeated inadequate dosage is one of the most remarkable phenomena brought to light by radiation therapy. The same relation has been observed for normal cells by Holthusen, who found that a dose much larger than an epilation dose was required to restrain the regenerat-

ing growth of hair in an epilated area of scalp. Acquired resistance of tumor cells is best illustrated in the cases of long-radiated tumors which recur in dense scar tissue. This condition may be called "abortive fibrosis." Here the tumor cells are protected against the attack by leukocytes and granulation tissue, and their metabolism is probably very low. Yet, the resistance may become so high that doses approaching the caustic type injure the stroma and the normal tissues, while the tumor cells survive. It appears that some tumor cells enjoy a capacity for adaptation to the effects of rays. Later they may exhibit very active growth, which we are inclined to refer to the loss of growth restraint in the over-radiated tissues and body. This theory must necessarily have a bearing on the plan of radiation therapy. The exact conditions under which it occurs require careful study. It does not seem to interfere with the successful results of moderate doses delivered over a long period in comparatively resistant tumors. It seems to be a sufficient basis for preferring to deliver the necessary dose as quickly as possible, especially when the total dosage required is high.

(9) *The natural history of tumors as a guide to radiation therapy.*—In planning the treatment of any resistant tumor, it is highly important to keep in mind the natural history of the tumor. We seldom see the natural history of most tumors, owing to interference in their early stages. It is a nearly universal assumption that all tumors possess unlimited powers of growth and that unless they are dealt with summarily they will continue to grow indefinitely. This assumption is not justified.

Many chondromas cease to grow after the bones have reached their normal full development. Many fibrosarcomas of bone enjoy only a very slow growth, continuing over many years without metastases. The natural history of the more aggressive giant-cell tumors of bone ends in death by hemorrhage and infection, but the less aggressive forms often cease to grow and spontaneously regress, sometimes after fracture. Under the present standard surgical treatment of mixed tumors of the salivary glands, these tumors have a rather high mortality rate from recurrence and local extensions, while in many others there is permanent deformity from loss of the facial nerve. Yet many salivary gland tumors have a limited growth capacity. Some of them cease growing after reaching a moderate size and remain stationary for as long as twenty-five years. This rule does not apply to the cellular carcinomas of the salivary glands.

Most subcutaneous neurofibromas remain indolent throughout life; some grow to moderate dimensions over a very long period, but give little disturbance to the patient, while others become pedunculated and may even be spontaneously extruded.

A considerable proportion of uterine myomas become cystic or fibrous or calcified. There is little opportunity to observe the natural tendencies of adenofibromas of the breast or of low grade adenomas of the thyroid gland, but there are old records of many of these tumors which show that they may cease growing after a variable period. The great majority of pigmented moles become fibrous, papillary, or pedunculated and remain harmless throughout life.

Even with frankly malignant tumors, it is well known that when they are not tampered with, the course may be very slow and continue for five, ten, or even twenty-five years without grave disturbance to the patient. Moreover, it is a well attested fact that incomplete removal of such tumors is often followed by recurrence in more malignant form.

When, therefore, one approaches the treatment of such tumors with the idea of complete surgical removal, or with the object of killing tumor cells with heavy radia-

tion, it should be remembered that while this object may be attained, yet if it fails the condition of the patient is generally rendered worse rather than better and that many benign are converted into malignant growths.

From this point of view, there would seem to be a large field for radiation treatment of benign tumors of uncertain prognosis with the object of restraining growth, limiting the size which the tumor may reach, preventing complications, rendering the condition practically harmless, but not attempting to cure the tumor in the radical sense. While this plan is not in accord with the modern tendency to secure quick and final results, very numerous cases can be cited to illustrate its great advantages to the patient.

When one radiates low grade neurosarcoma and then becomes impatient at the end of a few weeks or months because there is no result, and operates, he is not pursuing an intelligent plan. It has recently appeared that patience and persistence accomplish much more for these very dangerous and distressing conditions than formerly seemed possible.

Mixed salivary gland tumors often fail to show immediate response to radiation, but if one can reduce the growth capacity of these tumors by from 10 to 20 per cent, the final result after one year or more may be a harmless, quiescent, although persistent mass, which is far better than the loss of the facial nerve, and death from a recurrent infiltrating ulcerating tumor.

One of the first cases of recurrent spindle-cell periosteal sarcoma that I saw treated by radiation continued to grow for four months after heavy radiation, which had to be suspended. It stopped growing at six months, was regressing at one year, and then completely disappeared, never to recur.

I have been much interested in a case of huge lymphangioma of the tongue in a child one year of age, in which the tongue formed a large protruding ulcerating mass with an apparently hopeless prognosis. Persistent radiation gradually stopped the growth, while the natural increase in dimensions of the child's head and jaws eventually permitted the tongue to recede within the mouth, so that the child now, at the age of six years, is an extremely vigorous, healthy youngster. The only recorded cures of juvenile myxosarcoma of the nares and pharynx have been accomplished by long continued, persistent use of small doses of radium or X-rays, but the aggressive attack on these tumors by surgery or interstitial radiation invariably results in disaster.

The exact mechanism by which prolonged radiation affects the growth of resistant tumors is a matter requiring more careful investigation than it has received. There are probably several factors concerned, but it seems to me highly probable that the influence is mainly upon the blood vessels, which eventually shrink and cut off the blood supply. If the mechanism were more fully understood, it might be possible to plan the treatment more intelligently and to vary the dose so as to accomplish different effects in different tumors.

It is a well established principle, supported by clinical observation and experiment, that radiation invariably reduces growth capacity of cells and tissues, although months or years may elapse before its final effects become apparent. Based upon this principle, always controlled by sound clinical judgment and influenced by the natural history of the disease, efforts to control resistant tumors by radiation may well be pursued with the hope of enlarging the scope of successful radiation therapy.

TREATMENT OF MALIGNANT GROWTHS OF THE NASAL ACCESSORY SINUSES AND NASOPHARYNX[1]

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IT is not the purpose of this discussion to present a detailed review of all phases of treatment of tumors of the accessory sinuses and nasopharynx but rather to call attention to a few of the more outstanding factors in treatment. For the most part, attention will be directed only to the malignant growths in these locations.

Probably no location in the body presents so many complicating factors as are to be found centered immediately about the nasal passages. A wide range of tumor type is possible. The primary site or origin of growth is often difficult and frequently impossible to determine; bone and cartilage involvement is hard to define; interference with sinus drainage and infection give rise to inflammatory tissue which it is often impossible to differentiate clinically from tumor tissue. The peculiar anatomy of the paranasal sinuses favors inflammatory processes. How much this contributes as a predisposing cause in the development of many of the growths is, of course, not known: certainly it is an important factor. Inflammatory processes alter the normal type of tumor growth and influence unfavorably the protective cellular reactions in the surrounding normal tissue.

Mixed infection, with the resulting inflammatory processes, complicates diagnosis. It adds to the surgical risk and aggravates tumor growth. Osteomyelitis almost invariably accompanies tumor invasion of bone, interfering with the reaction to the physical agents of normal tissues about the growth. More patients with these involvements succumb to fatal infection than do those subject to the natural progress of the disease.

HISTOLOGY

The complex embryology of the parts under discussion affords opportunity of tumor origin from many developmental anomalies; hence a wide range of tumor type is met with. In his book on "Neoplastic Diseases," Dr. Ewing has enumerated thirty-seven varieties of growths found in or about the nasal passages, any one of which is capable of blocking them.

A great many of the growths falling in this general group are intimately associated with the maxillary antrum. Whether most of the tumors referred to as antrum growths are primary or are secondary extensions from other sinuses or the nasal passages is frequently not understood. Inflammatory processes often mask the true picture.

In our own experience, these cases are usually so far advanced that the exact site of origin cannot be determined with any degree of accuracy. In a group of 136 malignant growths of the antrum examined in our service between 1917 and 1929, 83 per cent were so far advanced as to be inoperable by radical excision of the superior maxilla. Under such circumstances of advanced growth it is obviously impossible to determine with any degree of accuracy what the actual primary site of growth was.

Carcinoma is the predominating type of tumor. A cylindrical cell carcinoma of adenocarcinomatous structure is most common in all of the sinuses. It is rapid in growth, bulky, and bleeds easily. It invades bone readily or may erode it from pressure. Consequently, with this type of tumor in both

[1]Read before the Radiological Society of North America, at the Fifteenth Annual Meeting, at Toronto, Dec. 2–6, 1929.

antrum and nasal passage it is impossible to determine the primary origin.

Squamous-cell carcinoma usually represents secondary invasion of the antrum, but may arise there primarily from lining membrane cells altered or flattened by some previous inflammatory process. In our series of cases just referred to, 39 per cent were of squamous-cell structure.

There are certain basal-cell structures, adenoid cystic epithelioma, cylindroma, or endothelioma, which are altogether less malignant and of slower growth than other types but are not usually recognized until late. Of our series, 7.4 per cent were of adenoid cystic basal-cell structure. Strangely enough, we have had a similar percentage of transitional cell carcinomas in the antrum. From the normal histology of the parts, one would scarcely expect growths of this type to be so frequent as far forward as the maxillary antrum.

Most of the so-called "sarcomas" of the antrum are in reality round-cell carcinomas of atypical structure, the result of chronic inflammatory changes in the lining mucous membrane. True sarcoma of the antrum and nares is angiosarcoma or myxosarcoma. Osteogenic sarcoma is rare, yet does occur and is usually easily recognizable radiographically. In our entire group of antrum cases, only 10 per cent were found to be sarcomas.

Mixed-, spindle-, and round-cell sarcomas of the turbinates, so called "fibrosarcomas," are not uncommon. Chondromyxosarcoma of the vault of the pharynx is met with occasionally in children.

These two last mentioned types of tumor are usually of slow growth and of a low grade of malignancy and hence are amenable in a high percentage of cases to direct surgical treatment, providing it is very thoroughly done. They do tend, however, to recur, with the usual persistence of a slow, adult type of growth, and terminate fatally more often than is usually visualized, through the associated infection which is frequently attendant upon such a process.

Lymphosarcoma may appear at almost any point in the paranasal sinuses but is practically always only a part of a more generalized disease. It is not improbable, however, that this disease frequently has its origin in the lymphoid tissue of the postnasal space. Its invasion of the sinuses, therefore, is from behind forward. Its rate of growth is usually so rapid that the exact origin can only be guessed at in the nasopharynx. It has been our experience that lymphosarcoma is second in frequency only to the transitional cell carcinoma which occurs in the lymphoid tissue adjacent to the fossa of Rosenmueller.

DIAGNOSIS

The symptoms and clinical course of the malignant diseases of the paranasal sinuses are too well known to merit discussion here except for emphasis on one point. The cases are almost invariably far advanced before a definite diagnosis is made. Speaking generally, the only symptoms which seem to arouse the consideration of newgrowth are those incident to the late stages of the disease, namely, nasal obstruction, with nasal discharge or persistent bleeding, or pressure symptoms, with gross destruction of bone. Mention has already been made of the fact that of 136 cases of newgrowths of the antrum, 83 per cent were so far advanced upon coming to us as to be inoperable even by total excision of the superior maxilla.

The more inaccessible the primary growth is to routine examination—and particularly the smaller the growth is—the later it is recognized. This is well illustrated by our experience with transitional cell carcinoma primary in the nasopharynx. This type of growth is characterized in most instances by a very small, and, for a time, slow growing,

frequently symptomless, primary growth. In our experience, it is the predominating growth in the vault of the nasopharynx and it is interesting to note that, of all of our nasopharyngeal growths, 73 per cent of cases showed metastatic involvement of cervical lymph nodes at the time of applying to us for treatment. In other words, the metastatic extensions to the disease were the first to call attention to the presence of newgrowth. It does seem that many of these processes are regarded as of inflammatory origin for too long a period, and that biopsy or earlier surgical exploration of more sinuses, keeping in mind always the possibility of newgrowth, would result in a saving of many of these cases. It is my impression that many of the preliminary operations done in and about the nasal passages in the presence of chronic inflammatory symptoms are rather poorly planned from a strictly surgical standpoint, and that in too many of them histological examination of tissue removed is ignored.

In our series of antrum cases, 59 per cent had a prolonged course of nose and throat treatment before definite diagnosis of newgrowth was made, and 45 per cent of them had had various local operations on the nasal passages which did not reveal the true character of the disease. The same was true in 44 per cent of our nasopharyngeal growths.

It has been our unfortunate experience that radiographs for diagnostic purposes have not been as valuable as one might ordinarily expect. They may lend a certain amount of influence one way or the other, but are usually not conclusive in differentiating between a strictly inflammatory process and newgrowth, except in the very late stages of the disease, where the differentiation is obvious to other and simpler means of examination. It is true that we have been dealing almost entirely with well-advanced and late stages of malignant disease, yet within this group, where determination of extent of growth is of considerable importance, we feel that diagnostic X-rays have been of real value to us in only about 5 per cent of the cases.

SURGICAL OPERABILITY

A review of the literature reveals rather few favorable results in the treatment of adult types of malignant growths in the sinuses. This is not surprising, for we realize that surgical principles as applied elsewhere can rarely be applied in the treatment of accessory sinus growths, except, perhaps, in excision of the upper jaw for early growths in the maxillary antrum without extensive bone invasion. Where the technical surgical approach to an adult type of malignant growth is either through or immediately adjacent to the tumor-bearing area, little can reasonably be hoped for by such a removal, and, unfortunately, this is almost invariably the case in operating about the nasal passages. The procedures in general represent little more than a modified curettage, and, since the exposure is frequently inadequate and the field often obscured by bleeding, the curettage is more apt than not to be incomplete. No wonder that the disease recurs so promptly.

From a serious and strictly general surgical viewpoint, therefore, malignant growths in and about the paranasal sinuses are all surgically inoperable unless a degree of mutilation is accepted, which, in almost every instance, would not be tolerated—at least until the disease had extended beyond the bounds of operability even by these means. It is probable that the palliative benefits of the average intranasal operation are due to the factor of drainage and that the actual removal of tumor tissue is only secondary. From a curative standpoint, therefore, operative surgery has rather little to offer.

The same anatomical hazards which defeat operative surgery in the treatment of this group of diseases are equally serious as stumbling blocks to successful treatment by irradiation. Unless a sufficient quantity of a proper type of radiation can be delivered accurately and uniformly to the tumor-bearing area, and unless the reaction to this treatment can go forward with a minimum of inflammatory complication, it is useless to employ irradiation with any hope of curative results.

It is here that the combination of surgery and radiation offers a possibility for dealing with a varied group of malignant diseases in complicated anatomical locations. It is possible to gain access to and to provide drainage from practically all of the locations under discussion by reasonable and relatively simple surgical procedures. Usually these can be carried out without disfigurement to the patient. Beyond that, the problem in most instances becomes one of proper technical application of the irradiation.

It is this principle of combining radiation for the treatment of the tumor-bearing area and surgical measures for access and drainage that we have attempted to follow in our work for the past several years. There has been gradual improvement in our various surgical methods of access, and, particularly with more accurate data on radium dosage and technical means of application, we feel that a reasonable hope is held out in a very considerable number of these cases which previously could be regarded only as palliative prospects at best.

DOSAGE

During the past year, a tremendous advance in the direction of dosage accuracy has been made through the efforts of my associates, Dr. Martin and Dr. Quimby. Their work is published in detail elsewhere so that only brief reference need be made of it here. They have calculated the actual intensity of dosage in a large series of successfully treated cases and have found that, for the more adult types of epithelial tumors, a dosage intensity ranging somewhere between seven and ten erythemas is apparently necessary for successful eradication of the disease. This, of course, is a very broad statement and requires qualification from numerous angles.

The next step was obviously the application of this to the treatment of cases, with the result that for a given case the dosage intensity was determined upon, and then, from the physical standpoint, the actual applicator dose or combination of applicator doses predicated upon a practical basis to provide the total dosage actually indicated.

Naturally, many factors enter into the decision of the dosage intensity for any given case. The more adult types of growth call for greater intensities; the more embryonal types, being more radiosensitive, require less.

The location of the growth has a great deal to do with determining, from the physical standpoint, the source of radiation and the type of applicator to be employed. As has been shown by Martin and Quimby, external irradiation about the head and neck, whether X-rays, heavily filtered radium at distance, or a combination of both, affords at best only about 200 per cent of an erythema in the various locations in which it is necessary to deal with primary growths. In certain locations it is even difficult to attain this degree of intensity by external applications only. In certain palliative procedures this may, of course, be all that is desired, but where permanent control of the disease is the objective, some other means of increasing the intensity of irradiation within the tumor-bearing area must be sought. This may be through the use of filtered radium emanation in gold capillary tubes, by heavily filtered tubes in rubber, or

by having a large quantity of emanation in a small heavily filtered sphere.

In deciding upon dosage in this manner, it is the responsibility of the Physical Department to select whatever type of radium or radon container is most practical to increase the intensity of radiation to the proper degree. We are rapidly approaching the point where responsibility for determining the combination of technical or applicator doses or, if you like, radiological prescription writing, is passing out of the hands of the clinician and is being added to the responsibility of the physicist co-operating in this work.

So far we have attempted, in all except strictly palliative cases, to deliver the total dose of irradiation within a period of four weeks. This means that where radon by implantation is employed following external irradiation, the external applications must be completed in the first fortnight so that the radon implantation can be made at the end of that time, since it is active for approximately a fortnight after implantation.

It is frequently possible to take advantage of a tumor-bearing area as a radium applicator, so adjusting the dose that surgical removal to provide more adequate drainage will be done as soon as the emanation has decayed. In case it is more desirable to provide the drainage at an earlier date, the initial dose of radon implanted can be increased and then cut short by the surgical removal before it has completely exhausted itself.

Post-operative irradiation in such a combination of surgery and irradiation is not, in our judgment, as desirable as pre-operative. In certain instances, however, it becomes obligatory. It is frequently not possible to implant radon with reasonable accuracy in certain of these growths without some preliminary surgical exposure. This is well illustrated in many of the growths primary in the antrum, which have invaded bone extensively and are extending in the direction of the orbit or ethmoids. Here, surgical cleaning out to facilitate drainage and at the same time to permit of access to the more inaccessible portions of the growth is essential, and is combined with immediate application of heavily filtered radium in some type of suitable heavily filtered applicator or, if the anatomical relationships are suitable, by radon implantation.

TREATMENT OF CERVICAL METASTASES

So far, we have considered in a general way only the treatment of the primary growths in this group of diseases. With many of them, however, treatment of the secondary extensions, particularly to cervical lymph nodes, is equally or more important than treatment of the primary tumor. For these we follow the same general principles as have been outlined previously for metastatic nodes secondary to intra-oral carcinoma—that is, a combination of X-rays, radium, and surgery.

All necks, in cases of metastasizing malignant growths of the paranasal sinuses and nasopharynx, are radiated with short wave length X-rays. If no nodes are palpable, the cases are kept under careful, periodic, routine examination. If an enlarged movable node with presumably intact capsule is present on admission or appears later, *in cases of epidermoid carcinoma,* the X-radiation is supplemented by radium packs, and, following this, a unilateral dissection is done under local anesthesia. Radium emanation is usually buried in the wound at the time of the surgical dissection. If the metastatic node has perforated its capsule and the infiltrating growth is fixed in adjacent structures, we class the case as inoperable. External irradiation is continued and emanation tubes implanted in the mass as a palliative procedure, but no dissection is

attempted. Likewise, if the primary growth is far advanced but with an otherwise operable neck, we treat the neck as well as the primary mass in a purely palliative manner. If the primary growth in the sinus is of basal-cell type, no attention to the neck is necessary because the tumor does not metastasize. If the primary growth be a lymphosarcoma, no surgery is indicated in the neck. It is a disease which extends widely and rapidly, and, as for any single local manifestation, it can always be managed better by the physical agents than by surgery.

As for the true sarcomas occasionally met with in the sinuses, I am of the opinion that no surgery is indicated when metastases are present. They are too apt to be multiple and had best be treated by radiation.

One group of the embryonal epidermoids should receive special mention in connection with their cervical metastases, namely, the transitional cell carcinomas. Their response to irradiation is more like that of the lymphosarcomas than of the adult epidermoids. External irradiation, or this plus radon implantation, is all that is indicated by way of treatment. This type of disease is apt to metastasize widely and to distant parts, so that in our judgment neck dissection has not the same prospect of permanent benefit that it has in the true acanthomas. Furthermore, the transitional cell carcinomas are locally quite radiosensitive and hence lend themselves, particularly as far as local or individual masses are concerned, to successful treatment by irradiation.

It is, of course, extremely difficult to appraise this plan of neck treatment, even though we have been following it now for several years. It is encouraging, however, to note that in our series of antrum cases 63 per cent had no nodes throughout their entire course, while only 16 per cent developed nodes after admission to the service. It would seem that the routine precautionary radiation had some influence in the direction of growth-restraint to palpably uninvolved necks.

CONCLUSIONS

1. Surgical exploration of the paranasal sinuses and biopsy should be resorted to earlier and more frequently, so that earlier diagnosis of newgrowths may be made.
2. With few exceptions, the principles applying to surgical removal of cancer in general cannot be carried out in dealing with growths in the paranasal sinuses.
3. Radium and X-rays are of value in treating this group of cases, but, except in palliative procedures, must be used in conjunction with surgery.
4. Radium and X-rays may be depended upon to eradicate the tumor tissue if applied accurately and uniformly throughout the growth in sufficient dosage.
5. Surgery must be employed to provide exposure for radium application and adequate drainage.
6. The anatomical relations of the parts are such that infection is a much greater menace here than in newgrowths in most other locations.

RADIATION TECHNIC FOR CANCER OF THE MOUTH WITH COMBINATIONS OF GAMMA RADIUM RAYS AND VARYING QUALITIES OF HIGH VOLTAGE ROENTGEN RAYS[1]

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TECHNICAL methods of radiation and dosage must be developed as carefully as the details of a difficult operation. Unless treatment is planned so that all parts of a cancer-bearing area receive a uniform distribution of radiation, with intensities sufficient to destroy cancer cells, then any radiation procedure is fundamentally inadequate to cope with the disease, and the case will not get the benefit of any virtue which efficient radiation may otherwise hold out for the particular histological character of a given growth.

The value of roentgen ray and radium in the treatment of early cancers, particularly early cancers of the skin and mouth, and more particularly the early epidermoid cancers of the cervix, is incontestible: even some very advanced cancers have shown remarkable regression. These improvements are increasing in number with progress in technic, together with a more general enthusiasm and systematic clinical application of established physical principles, and the free communication of experiences between institutions throughout the world.

While cancer of the esophagus and gastrointestinal tract, hypernephroma, and brain tumors have been particularly refractory to radiation, the value and limitations for good in advanced cancer, particularly of the skin and intra-oral and pelvic lesions, are fully recognized.

The fact that early cancers have responded to a manifold variety of technics has long been recognized as evidence of a difference in the sensitivity of different types to radiation. The marked variation in the cellular structure of epidermoid carcinomas led to Broders' (2) investigation, with grading of tumors into four groups according to the degree of cellular differentiation. Later, Healy and Cutler (7) brought out the striking paradox that with radiation treatment the prognosis is better with the higher grades of malignancy, because the radiosensitivity increases with the malignancy.

Ewing's (4) observations on the radiosensitive carcinomas have been most elaborate and painstaking. This information explains much of the wide variation of responses of many lesions similar in location and extent of involvement to similar types of radiation treatment. He states that "The derivation of squamous carcinoma from adult squamous cells undoubtedly determines the adult resistant characters of the tumor cells. An extensive group of epidermoid carcinomas arise from stratified epithelium which does not produce keratin or horny material and is called transitional epithelium. This tissue lines the upper uterine cervical canal, the trachea and portions of the larynx, the nasal passages, and the ducts of many glands opening on mucous surfaces. An extensive group of epidermoid carcinomas develops from such epithelium and they regularly exhibit considerable sensitivity. It is, however, often difficult to determine whether a tumor arises from

[1]From the Radiological Department of the Philadelphia General Hospital, Philadelphia. Presented before the Radiological Society of North America, at the Fifteenth Annual Meeting, at Toronto, Dec. 2–6, 1929.

transitional epithelium or from squamous, because metaplasia may yield squamous cells in transitional cell tumors, and squamous tumors may be very anaplastic and fail to produce keratin. In the intra-oral group especially, the influence of anaplasia and metaplasia renders the pursuit of histogenesis very uncertain, so that the influence of this factor on sensitivity cannot well be estimated."

Many apparently early mouth cancers, from the standpoint of surgical operability, have been resistant to intensive roentgen-ray and radium treatment, and have developed uncontrollable gland metastasis even after apparent adequate local and regional treatment. In many instances a clinical cure of the primary lesion has been obtained, even with gland metastasis present at the start of treatment. More than 60 per cent of our mouth cancer cases had advanced local and gland involvement at the beginning of treatment. Unless some definite radical technical procedure can offer a further improvement in the end-results of these advanced cases and the early resistant cases, then radiation results must continue to be evaluated in the light of "palliative benefits."

THERAPEUTIC PROCEDURES

Some early mouth cancers have been cured by surgery, cautery, electrodesiccation, radium element in steel or platinum needles, or radium emanation (radon) in gold "seeds" buried into and about the cancer area, as well as surface applications of radium in contact with the lesion. It is now generally agreed that intra-oral cancer is best managed by irradiation (X-ray or radium or both), and sometimes in conjunction with surgery, particularly when there is gland involvement.

In mouth cancer with gland involvement Quick (11) does a complete unilateral neck dissection, with radium "implants" scattered about suspicious points of the wound. He makes no attempt to dissect inoperable nodes.

Regaud (14), at the Curie Institute of Paris, advises removal of enlarged cervical glands by radical *bloc* resection in lip cancers. For cancers of the mouth such resections are done even when glands are not palpable, but if gland invasion from mouth cancer has already taken place, according to microscopical studies, then *bloc* dissection is not done, but treatment is confined entirely to heavy external radium packs.

Of 160 cases of cancer of the mouth, Forssell (6) reports 72 with lymph node metastasis. In none of the 72 cases was there a single one-year cure from radiation alone. When surgery of the glands was combined with radiation he obtained 35 per cent three-year cures, and 30 per cent five-year cures (10 out of 27 cures).

Ewing (4) feels that the practice of leaving nodes until they show clinical signs of involvement seems to be justified in view of our present resources from radiation.

Implantation of radium directly into a single enlarged node, or dissection of a single node if not fixed, have not been popular procedures, but have shown good results, and are justified in selected cases, particularly when the age or physical condition of the patient or the great extent of the primary lesion demands conservatism.

When the question of gland involvement is considered, much stress must be laid on soft, fixed, and infiltrating characteristics, conditions which should readily establish surgical inoperability. Most observers consider a case with bilateral gland involvement as beyond any therapeutic procedure for cure.

We routinely radiate both sides of the neck in all intra-oral cancers, with or without gland involvement. A single firm and freely movable gland is occasionally subjected to a simple excision, but only if it resists intensive cervical radiation or develops after apparent adequate cervical radi-

ation. Surgery for enlarged glands is now generally limited to the lip, cheek, and floor of mouth cases, and only if the primary lesion is within the scope of curability according to our experience with radiation procedures.

SHORT WAVE LENGTH RADIATION

If the biological results of radiation are the effects of a direct action, then some outlook for improving the results in these advanced cases may be had by further increasing the total quantity of radiation. Theoretically the ideal type of radiation is that which causes effective regression of a tumor and at the same time preserves the surrounding normal structures. Many failures are undoubtedly due to insufficient dosage and faulty distribution.

Interstitial radiation will always be complicated by difficulties in getting an exact and uniform distribution of the radium "points." Inability to accurately estimate the scattered and secondary radiation effects in the tissues is outweighed by the information Cutler obtained from histological studies of tissues after varying intensities of radium. Failla (5), Quimby and Pack (12) have established doses with gold filtered radon "seed" implants which are practically within a range of mathematical precision. The clinical application of these data by Quick (11) has shown most gratifying results.

Implantation of radium into and about a neoplastic area is not without danger of tearing tissues and opening up vessels that may lead to metastasis. For this reason we precede interstitial radiation with surface contact radium applications in divided doses over a period of about ten days.

Even with platinum and gold filtration for the radon seeds, the good results are probably an effect of radiosensitive types of cancers, or the caustic effects in the more resistant cases. Our own experience with interstitial radon with 0.2 mm. of gold filter has been very encouraging in selected early cases. We believe its use is largely limited to the floor of the mouth, tongue, soft palate, and tonsillar region and occasionally the cheek. When the local lesion is surgically inoperable, with gland metastasis, then external radiation and surface applications directly in contact with the lesion and surrounding normal structures will prove as adequate as the interstitial treatment.

Lacassagne (9) maintains that unless we admit the destruction of certain kinds of malignant cells by the elective action of roentgen rays and gamma rays of radium, then we should give up the radiotherapy of malignant disease as manifestly inferior to other therapeutic methods. The gamma rays of radium are ordinarily considered as those resulting from filtrations equivalent to 2 mm. of brass or 0.5 mm. of platinum. By the use of 2 mm. of platinum or its equivalent the erythema value is two and a half times greater. While there is no proof of a difference in the biological effect of different qualities of rays, there is a vast difference in the penetration.

Wood (16) concludes from many animal tumor experiments that there is no difference in the lethal effect of long and short wave length radiation. Chamberlain (3) and Holthusen (8) maintain that 500 r with different wave lengths will produce the same biologic effects. This biologic effect may be parallel to ionization in air, but the absorption changes with the wave length according to its penetrative power, which must necessarily alter the distribution of the radiation intensity.

Because of the lessened skin absorption with short wave length rays, Russ and Scott (15) observed that the skin and tumor reactions from short wave length rays did not equal the soft wave length rays until six times as much energy of the short wave length rays had been absorbed, but to cause

the same effect with two groups of wave lengths, only 2.6 times as much energy of the short wave length had to be absorbed.

Because of the recognized increased tissue tolerance and greater penetrative properties of short wave length radiation, the treatment of deep-seated growths with these qualities of rays is a paramount consideration. If prolonged treatment over a period of time is necessary, the tissues are limited in their tolerance for the soft or long wave length radiations.

TECHNIC OF RADIATION OF NECK

In order to fulfill a program that would permit the delivery of greater quantities of radiation to the tissues, two types of radiation were employed on the skin: a combination of roentgen ray, 200 K.V., and 0.5 mm. of copper, and radium packs with a filtration of 3 mm. of lead and 0.5 mm. of silver. This amount of lead and silver has a density equivalent to 2 mm. of platinum or gold. It was found that the combination of these two types of radiation, divided over a period of two weeks, permitted 120 per cent of a dose of roentgen rays and 125 per cent of a dose of radium on the same skin area. These factors equal a total of 245 per cent, an erythema with combined radiation to each side of the neck, or a total of nearly 500 per cent to both sides, with a resulting depth dose in the average neck of 2½ erythema skin doses. The erythema is intense and appears in about twenty-one days and lasts about ten days. In certain advanced cases this radiation has been carried out more slowly (saturation technic, 10) and has been extended for from four to six weeks. Divided doses over this period of time have permitted as much as 350 per cent of combined (X-ray and radium) radiation to a single skin port without damage. The radium packs are 10×15 cm., with 4 cm. distance. If this pack is given at one sitting, the erythema dose is 15,000 millicurie-hours. If divided into four sittings of 48 hours each (5,000 millicuries), a total dose of 20,000 millicurie-hours can be given. Quimby and Pack (13) observed an increased skin tolerance with combinations of different wave length radiations ("soft" and "hard").

Our routine treatment in intra-oral cancers, therefore, is to plan four radium packs of 48 hours each (total 5,000 millicurie-hours) to each side of the neck, making a total of eight packs, with a total dose of 40,000 millicurie-hours. This makes a total time of 384 hours. On the day of rest between radium treatments a roentgen-ray treatment is given to each side of the neck. A total of six 20 per cent doses is given to each side of the neck. Sometimes radium packs alone are used, and as much as from 50,000 to 60,000 millicurie-hours have been given to both sides of the neck in from six to eight weeks, or 15,000 to 30,000 to a single skin port.

TREATMENT OF PRIMARY LESION

Surface applications of radium are made in contact with the lesion and surrounding structures. If the involvement is not greater than that which might be considered as surgically operable, radon in 0.2 mm. gold seeds is embedded into and about the region involved. The full intensity and homogeneous distribution of interstitial radiation is given, but the contact surface applications are not carried to the height of a local reaction—approximately 75 per cent of an erythema dose.

For the advanced cases with local involvement, we believe that surface applications of radium with heavy filtration will be effectual in causing retrogression and palliation with as much certainty as can be accomplished with the interstitial radiation. The use of 2 mm. of platinum admits of

wave length rays more penetrating and less caustic than 0.5 mm. of platinum or its equivalent of 2 mm. of brass, which is the common thickness of filter in general use. For economical reasons the use of lead was selected. These lead capsules can be made wall thickness of 4 mm. to make up an equal density with the lead applicators.

DESCRIPTION OF APPLICATORS

Figure 1 illustrates a combination of applicators fixed to lead strips, or handles, 3

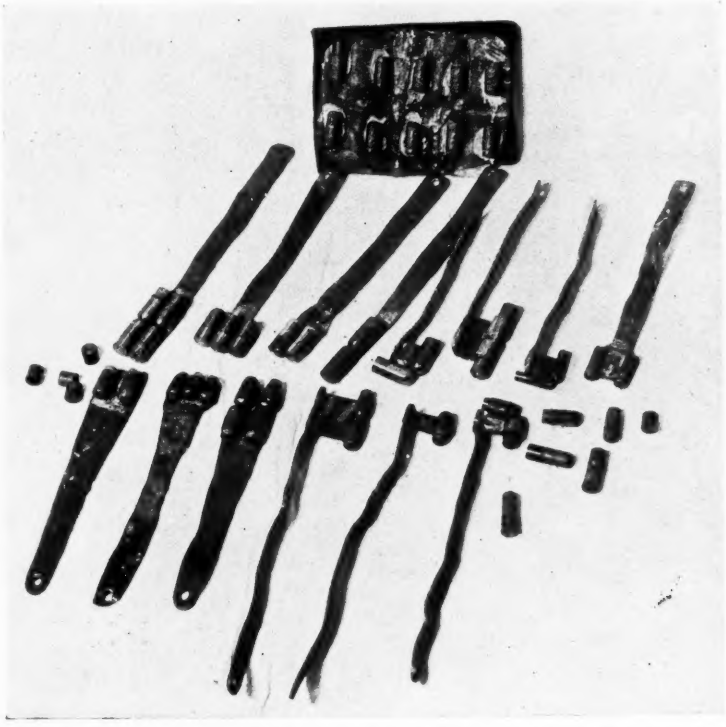

Fig. 1. Stock applicators made of lead; wall thickness, 3 mm. The plaque of ten capsules fixed on a copper plate (0.25 mm. thick) maintains a uniformity and simplicity of application. This same arrangement of applicators made with brass of different thicknesses is also used.

to fit any size or number of needles or radon tubes. The radon glass seeds are delivered to us in silver tubes 0.5 mm. thick. The walls of the lead capsules are 3 mm. thick, equivalent to 2 mm. of platinum. All applicators are covered with three layers of pure vulcanizing rubber, 1 mm. thick. The distance from the radium point to the tissues is 5 mm. Because the lead capsules dent and become distorted after long use, they have been duplicated in brass, with a mm. thick. These have been arranged and fixed on copper pegs so that any adjustment on any location of a cancer of the mouth can be adequately made. When these capsules are covered with rubber they are 1 cm. in diameter and are not amenable to easy adjustment with dental molds. We have found that molds are excellent for contact applications, but when large groups of cases are to be treated, and the divided doses are used, then the dangers of prolonged ex-

Fig. 2. Pegged capsules approximating the contour of the floor of the mouth and the surface under the tongue; also the alveologingival folds.

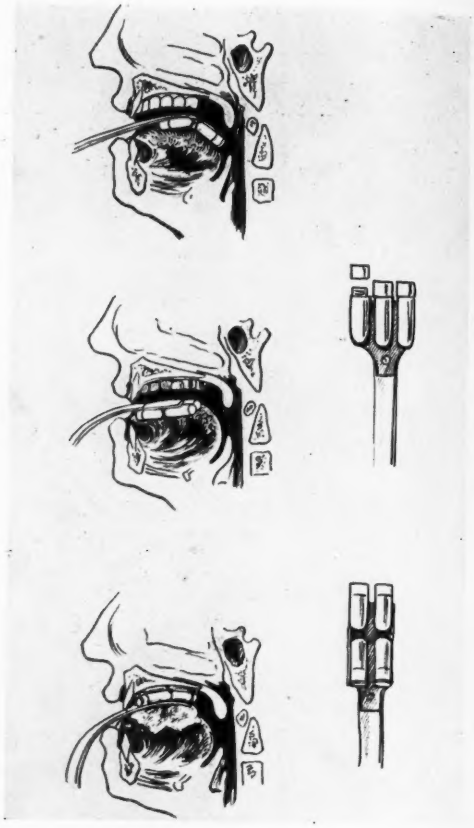

Fig. 3. Stock plaques applicable to the dorsum of the tongue, the roof of the mouth, and the cheek.

posure and careless handling become serious factors for the personnel of the department.

Figures 2, 3, 4, and 5 illustrate the various positions that are easily attained. The posterior aspect of the tongue and tonsil are treated after thorough anesthesia with swabs of a 5 per cent solution of cocaine. A rubber band to hold a small gauze pad on the back of the applicator not only insures good fixation by its wedge effect, but serves as a biting point to maintain a position. The peg or prong effect forces the lead capsule into the floor of the mouth, approximating the anterior group of cervical glands. These are made up speedily and accurately and with little danger to the technician. The planning of a treatment with assistants and nurses is facilitated, and a uniformity of technical procedures is developed by an almost automatic and routine system. The "pegged" arrangement of the capsules for stock applicators is varied with single capsules, or double capsules in parallel or at right angles to meet adjustments against the glossopharyngeal fold, the cheek and anterior pillar, or the craters of the upper or lower alveologingival folds. Flat applicators with one, two, three, and four capsules are easily adjusted against the cheek, palate, and dorsum of the tongue.

For external pack treatments a series of copper plates (0.25 mm. thick), 10 by 15

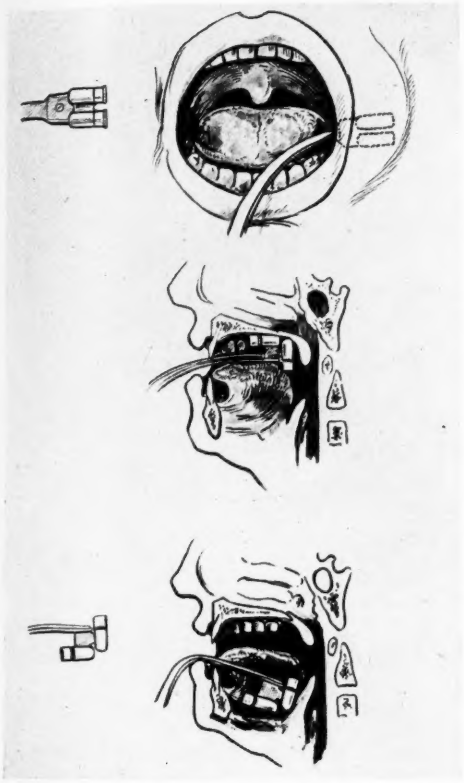

Fig. 4. Pegged capsules at right angles are readily adjustable to the floor of the mouth, against the glossopharyngeal fold, and in the crater of the alveologingival area between the upper jaw and the check.

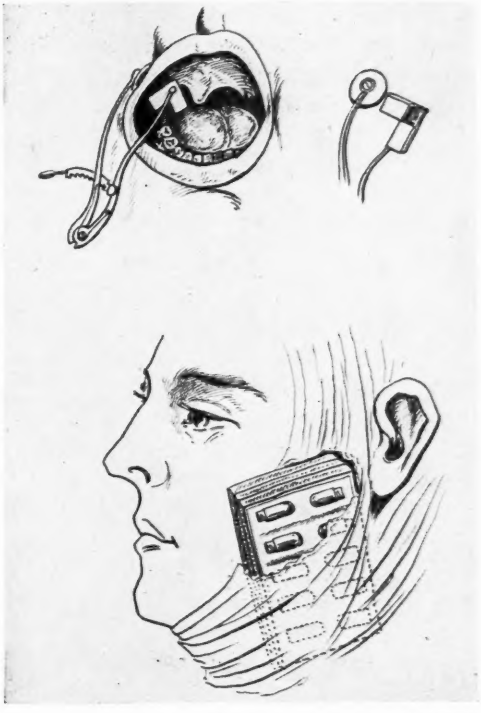

Fig. 5. Tonsil applicators made of brass 2 mm. thick (*above*). Routine fixation of radium pack (*below*).

cm., have been mounted with 10 capsules, distanced so that a homogeneous photographic density is obtained at 4 cm. radium point to skin distance. An average of 100 to 125 millicuries is loaded into a pack, which is routinely applied for 48 consecutive hours, giving an approximate average dose of 5,000 millicurie-hours. As stated above, this filter and distance of pack gives an erythema with 15,000 millicurie-hours (continuous radiation at an initial intensity of 250 millicuries). Ten to fifteen packs can be kept in constant service (with a 2 gram emanation plant). One of the ten capsules on the copper plate has a bore of twice the caliber of the other capsules and a wall thickness of 4 mm. of lead, so that weak tubes of radon can be removed from the silver capsules and loaded into this extra sized capsule. Six to twelve weak glass tubes can thus be passed along to their complete decay. The lead capsules have a loose brass cap with a lead cap 3 mm. thick. All applicators are fixed in a small vise attached to the technician's lead radium shield, and the caps are fixed in position with small strips of adhesive. The brass applicators have been made with screw caps.

The value of contact applicators to fit every location of mouth cancer lies largely in the conservatism of the method in weakened and advanced cases and the ability to use heavy filtrations that eliminate caustic action. It is this principle that is responsible for the working out of this arrangement of surface radiation in mouth cancer, and has permitted the delivery of greater quantities of radiation to the deeper tissues with the

heavier filter. The increased intensity is about two and a half times greater with 2 mm. of platinum than with 2 mm. of brass, and admits of prolonged treatments, following the experience and recommendations of Regaud.

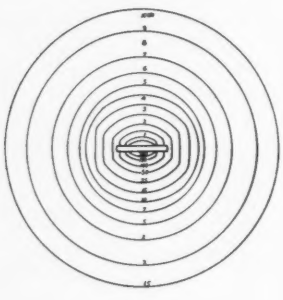

Fig. 6-*A*. Distribution chart of a radium capsule surrounded by tissue; 1.5 mm. brass filtration, 500–1,000 mgm.-hrs. applied; erythema dose designated by 100. (*After Bachem.*)

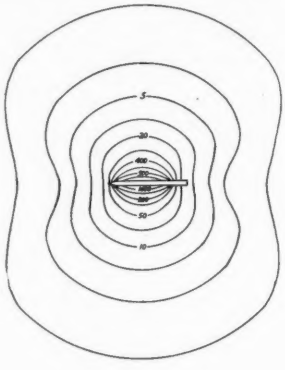

Fig. 6-*B*. Distribution chart of radium needle, surrounded by tissue; 50–100 mgm.-hrs. applied; erythema dose designated by 100. (*After Bachem.*)

The lead capsules with 3 mm. walls and 0.5 mm. of silver produce an erythema with 350 millicurie-hours in one sitting. If this application is divided over a period of ten days, in amounts of 150 to 200 millicuries, a total dose of 1,000 millicurie-hours can be given. Bachem (1) has estimated a depth dose of approximately 50 per cent at 2 cm. depth, with a surface dose of from five to ten erythemas with 1.5 mm. of brass (see Figs. 6-*A* and 6-*B*).

Ionization measurements are not adequate for determining radiation values with filtrations as great as 2 mm. of platinum. Short wave length rays admit less scattered and secondary radiation, but the penetration theoretically is greater, and the tissue tolerance extraordinarily greater, so that a total dosage from three ports about a tongue (Fig. 7) is equal to approximately five erythema doses in the center of the tongue. When this is combined with the external radiation through the neck on both sides, the total radiation in the tongue will reach six to eight erythema doses. The dorsum and under surface of the tongue will be given approximately 3¼ E.S.D. to each of three areas. The plaque of three and four applicators on the dorsum of the tongue requires 1,500 to 2,000 millicurie-hours because of its larger area. A dose of 1,000 millicurie-hours to each area on the floor of the mouth gives a total dose from three ports of 3,000 to 4,000 millicurie-hours. If the posterior aspect of the tongue is treated, an additional 1,500 to 2,000 millicurie-hours will be given. It is significant to point out that each "point" area must be treated with divided doses. We average four applications to each area. Lesser filtration with this intensity of radiation is dangerous and will probably produce a radiation necrosis. Frequently a very advanced cheek or tongue lesion requires further treatment and generally an additional 1,000 millicurie-hours is added. This represents the total for a given area, and when the dorsum of the tongue and the floor of the mouth on both sides are treated, a dose of 5,000 to 6,000 millicurie-hours, 0.5 cm. distance, will be attained with additional treatment, which thus far has been used only in very advanced cases.

The local reaction is marked and usually affects all parts about the area treated. The intensity of the reaction is about equal to the local effects about the cheek, roof of mouth, and tongue following interstitial radiation of the tongue with radon (gold seeds). The reaction appears in about two weeks, which is sooner than with the external surface pack radiation, but the total intensity of radiation is much greater.

We are recommending contact surface applications of radium as another procedure, not to supplant the interstitial use of radium but to supplement it in the early cases, and to use it entirely in the advanced cases, particularly where palliative benefits at most can be expected. We urge the use of surface applicators where large doses are desired, because, with the heavy filtration, increased depth doses can be attained without danger of slough and with a possible outlook of good results such as are not ordinarily obtained with the softer type of radiation.

This technic has been followed for a year. Greater doses are gradually being reached. In many instances there are regressions such as were not obtained with the softer or longer wave length radiation. It is impossible to make a statistical evaluation of advanced cases treated according to this technic up to the present time. Clinical impressions indicate an improvement of sufficient extent to justify intensive procedures along the lines of increasing the total amount of radiation in the tissues. The blood and physical condition of the patient must be considered.

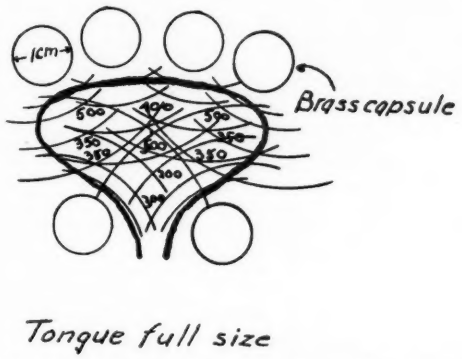

Fig. 7. Illustrating the distribution of intensity of radiation through cross-section of tongue from three surfaces. Brass and lead filters equivalent to the density of 2 mm. of platinum permit a total of 3 erythemas on each area, with an approximate depth dose of 5 E.S.D.

CONCLUSIONS

1. The success of the radiation treatment of intra-oral cancer depends upon the degree of radiosensitivity of the lesion.

2. This sensitivity is noted by rapid responses to radiation as well as histologically by the degree of cellular differentiation—the more highly cellular, the more highly malignant, and, conversely, the more radiosensitive.

3. Improved results in the radiation treatment of advanced cancer of a resistant type will necessitate the administration of still greater quantities of radiation.

4. The use of additional radiation must depend upon short wave length rays, because of their greater penetrative properties, with a definitely increased skin tolerance.

5. The tissue tolerance is still greater with combinations of short wave length rays. No elective action of different types of rays is conceded.

6. Various treatment procedures are discussed.

7. Description and application of an assortment of stock radium containers to meet the requirements of a lesion in any part of the mouth.

8. By external and contact surface radiations alone, five to eight erythema doses can be administered through the center of the tongue.

9. Radium filtrations, with densities equivalent to 2 mm. of platinum, are advocated. This is approximately two and a half times greater than the usual filter of 2 mm. of brass.

10. The success of the radiation treat-

ment of advanced cancer will depend upon such technical procedures as will eliminate dependence for good results on the so-called "caustic effects."

11. Clinical impressions indicate that combinations of short wave length radiation will improve the end-results in advanced and resistant types of intra-oral cancer.

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ADVANTAGES AND LIMITATIONS OF EXTERNAL RADIATION IN THE TREATMENT OF RECTAL CANCER[1]

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EXTERNAL irradiation with radium and high voltage roentgen rays plays an important part in the present-day treatment of rectal cancer. This type of radiation is capable of producing an eradication of the disease in tumors of the most radiosensitive nature, and varying degree of growth-restraint in those that are more radioresistant. It is the ideal form of radiation in that no trauma is produced and no infection introduced into the tumor or surrounding tissues. The beam of radiation includes a larger area of lymphatics than can be reached by surgical dissection or by other forms of radiation. An improvement is frequently noted coincident with the beginning of treatment. Seldom is the constitutional effect upon the patient sufficiently severe to interfere with his daily routine.

Nevertheless, in spite of the fact that external radiation exerts a beneficial effect upon rectal cancer, it should be considered as only the first step of radiation therapy and not an individual method of treatment. Further radiation is required in over 80 per cent of cases. The limitations of this method are largely due to (1) the radioresistant nature of rectal carcinomata, (2) the depth of these tumors and the degree of tolerance of the skin to radium and roentgen rays.

There is a slight variation in the depth of tumors and in the tolerance of the skin to irradiation, while the radiosensitivity of rectal cancer varies widely. The varied histology of early uncomplicated growths is such as to suggest at once a wide range in the probable radiosensitivity. With the onset of deep-seated infection and ulceration, the importance of this factor is greatly reduced. Infection spreads more rapidly in cellular or anaplastic cell carcinomata than in the more adult types. The tolerance of the skin to irradiation appears to be influenced by its vascularity. Usually, the skin of the thin anemic patient will withstand larger dosage than that of the obese. The percentage of the skin dosage which reaches the tumor mass depends upon the size of the pelvis and the location of the growth.

High voltage roentgen rays have been extensively—in fact, almost exclusively—employed for this form of therapy. Experimentally, there does not appear to be a great difference in the effect of high voltage roentgen rays and the gamma rays of radium. Clinically, however, there is a marked advantage afforded by the gamma rays. Since the 4 gram radium element pack has been added to the Memorial Hospital equipment, so that external radium irradiation could be more freely employed, there has been a marked improvement in the effect produced on rectal cancer by external treatment. Nevertheless, this amount of radium is sufficient for only a small number of the patients applying for treatment: except in selected cases, it has been necessary to supplement a part of the applications by high voltage roentgen rays. The combined use of radium and roentgen rays, in which radium forms the greater part of the dosage, has its advantages. There is an unlimited supply of roentgen radiation available at a comparatively low cost. A considerable percentage of the dosage, when desired, can be given within the first week of treatment. The short time required to administer an erythema dose of roentgen rays by the water-cooled machine is greatly appreciated by the

[1]Read before the Radiological Society of North America at the Fifteenth Annual Meeting, at Toronto, Dec. 2–6, 1929.

nervous and debilitated patients who find it rather trying to lie quiet in one position for a two-hour daily radium application. By combining the two agents (1) a larger dosage may be administered at the site of the tumor, because of the increased tolerance of the skin to the two methods.

Radium radiation is given at 15 centimeters from the skin by means of the element or emanation pack. Sufficient filter to eliminate all but the most penetrating gamma rays is employed, and lateral screening to prevent undue body irradiation. Usually, two portals of entry, an anterior and a posterior, are employed in routine radium applications. The number of portals is increased to three or four when larger dosage of gamma radiation is desired. Because of the shape of the pelves and the location of the tumors, the dosage of gamma radiation is not increased in proportion to the number of portals employed.

High voltage roentgen rays are administered through six portals, which include the greater part of the circumference of the pelvis. When tumors are situated low in the rectum, a perineal field is also employed. The usual factors of these applications are: 60 minute exposures, 185 kilovolts, 50 cm. skin target distance, 4 milliamperes of current, filtered by ½ mm. of copper and 1 mm. of aluminum. The time of exposure may be extended from 60 to 80 minutes, or, if a water-cooled machine is employed which operates at 30 milliamperes, the time of exposure is correspondingly decreased.

The actual percentage of the skin dosage which reaches the center of the tumor may be calculated from careful measurements. A tumor of the mid-rectum in a pelvis of medium size receives about 1.75 per cent of the skin dosage at each one of the seven portals. The same tumor will receive about 70 per cent of a skin dose of gamma radiation when the radium pack is applied over medial anterior and posterior fields. Therefore, when erythema doses of roentgen rays and gamma rays are administered over seven portals, the total amount of radiation which the tumor will receive is between 2.25 and 2.50 erythema doses.

The dosage and technic of application will depend upon clinical and pathological factors, which indicate the part that external radiation may be expected to play in bringing about the result. For simplicity of description, cases are separated into two groups: (1) those in which external radiation forms the first step of radiation therapy and (2) those in which external radiation is the only radiation therapy required.

There are three classes of cases in which external radiation constitutes the first step of radiation therapy, the cancers in all instances being comparatively radioresistant. These cases are classified in accordance with the result expected, by supplementing external radiation with other forms of treatment, into the following groups: (1) patients that present the possibilities of a clinical cure; (2) patients in whom a high degree of palliation is expected; (3) patients in whom only a moderate degree of palliation can be anticipated. The first two groups are given heavy preliminary external radiation, while the latter group receives a smaller amount. By heavy dosage is meant a pelvic cycle of roentgen rays consisting of seven portals, and radium applications of from 60,000 to 75,000 milligram-hours over each of two or more portals. The roentgen-ray applications are given daily or on alternate days and are followed by daily applications of 8,000 milligram-hours of radium until the full dose has been delivered.

This dosage produces varying degrees of alteration in the primary tumor. The majority of growths show a reduction in size, a lessening or disappearance of the ulcerating area, while the external limits are more

easily defined. Occasionally, a fixed tumor will be found to have become movable. These changes indicate a marked growth-restraint and a decrease in the degree of infection and surrounding inflammatory reaction. This local improvement is accompanied by a decrease in symptoms and an improvement in the general physical condition of the patient, favorable changes which facilitate further radiation therapy and offer an additional advantage to surgical interference, should the latter procedure be deemed advisable.

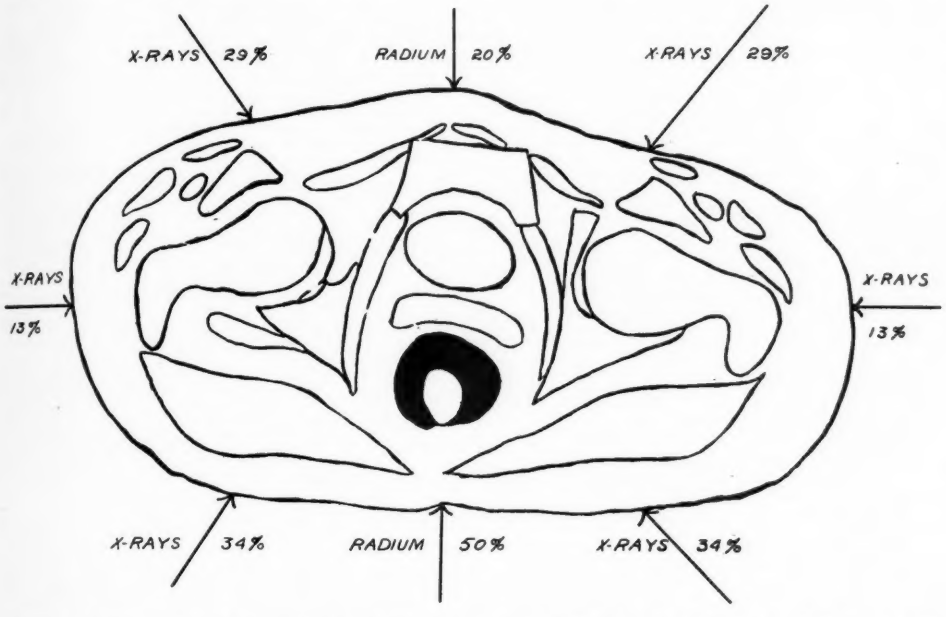

Fig. 1. Cross-section of a medium sized pelvis showing the direction of beams of radiation, with the approximate percentage of skin dosage absorbed in the center of the tumor.

While heavy preliminary external radiation is most valuable in the above two groups, a more satisfactory result is obtained in cases suitable for only moderate palliation by employing smaller preliminary dosage. This type of case usually receives a pelvic cycle of roentgen rays, with an interval of two or three days between applications. After about one week, radium applications are commenced, the total dosage for each portal seldom exceeding 50,000 milligram-hours. Patients in this group are in a less favorable physical condition and may not be able to withstand intensive applications. The object is to reduce the severity of symptoms, make the patient more comfortable, and, whenever possible, to prolong life. This is obtained with least embarrassment to the patient by moderate dosage of external radiation repeated at varying intervals, together with small repeated doses of interstitial radiation. Small preliminary external doses allow the patient to gain in weight and strength so that further treatment may be undertaken. Moreover, the skin will stand a much larger amount of irradiation when the applications are extended over a long period of time. Fractional doses may be repeated at comparatively frequent intervals. However, careful consideration must be given to the skin in all instances. Permanent damage is more apt to be done by small repeated doses than

by a large preliminary application, particularly if the fractional doses are prolonged over a considerable period of time.

There are two groups of cases in which external radiation may be used as an individual method of treatment: the most favorable and also the most unfavorable cases of rectal cancer. By the "most favorable" is meant cases in which a clinical cure of many years' duration may be obtained by this comparatively simple form of therapy. The cancer cells in this group are sufficiently radiosensitive to be eradicated by 200 or 250 per cent of an erythema dose of radiation. The number of these very radiosensitive cancers is small, being less than 1 per cent. The dosage and technic in this type of case correspond to that which has been described above as heavy external radiation. There is an early response to treatment and patients are free of symptoms after a few weeks, although it may require several months for the preliminary mass to completely disappear.

The most unfavorable cases receive the greatest amount of palliation from external radiation. Because of the extent and nature of the disease, and the poor physical condition of the patients, other forms of radiation are contra-indicated. These debilitated patients often show considerable temporary improvement following adequate dosage of external radiation. The dosage and the intervals between applications are governed by the condition of the patient and the response to treatment. This does not mean that all very advanced cases should be treated by irradiation—a certain number, unfortunately, are too far advanced for any worth-while palliation by any form of treatment.

SUMMARY

1. External radiation constitutes the first step in radiation therapy of all rectal cancer, and in certain selected cases may be the only form of treatment necessary.

2. The effect of external applications is limited by the depth of the tumor, the tolerance of the skin to irradiation, and by the radioresistant nature of the majority of rectal cancers.

3. External radium radiation is more effectual than high voltage roentgen rays. The two types of radiation may be combined advantageously.

4. The dosage and intensity of application are governed by the clinical and histological features of the case.

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RESULTS OBTAINED IN THE TREATMENT OF CARCINOMA OF THE CERVIX UTERI WITH RADIUM AND ROENTGEN RAYS FROM 1915 TO 1924, INCLUSIVE[1]

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IN this report we are compiling the results of treatment of carcinoma of the cervix with radium, considering only cases treated at least five years ago. All cases in which treatment with radium was employed at The Mayo Clinic for the ten-year period from 1915 through 1924 are included. This paper is supplementary to the report given in July of this year at the meeting of the American Radium Society (1); we are now adding our 1924 results.

During the decade mentioned, 1,094 patients were treated, 1,001 (91.5 per cent) of whom have been traced. We have separated the cases into four major groups: operable, borderline, inoperable, and modified. The modified group includes all cases in which the lesions were modified by previous treatment before we first saw the patients; previous treatment may have been by operation, cautery, radium, roentgen ray, or other means.

In the course of this ten-year period no treatment was applied in 167 cases, due to various reasons, such as recent treatment elsewhere or moribund condition of the patient. In 132 cases, operation, treatment by cautery, or treatment by some other method was carried out at The Mayo Clinic; however, irradiation was not done in these cases. These surgical measures, without irradiation, were applied during the earlier years represented in this review. In 1924, the last year considered, only three patients who were operated on did not receive radium.

We will not discuss details of treatment, except to say that the usual complete treatment employed in the inoperable group consists of six to eight applications in all, given, in turn, interstitially, intracervically, within the uterus, and vaginally. The total amount of irradiation is 5,000 to 6,000 milligram-hours. This is given over a period averaging three weeks, and is followed by a course of high voltage roentgen-ray treatment. Detailed factors in treatment have been given in a recent article (2).

Table I gives the age incidence according to groups. In Table II we have listed the number of survivors in all groups by years. Thus, twenty-nine patients treated in 1924 have survived five years, forty-two treated in 1923, twenty-nine in 1922, and so on down to our first year, 1915, in which group one patient survived five years. The right-hand column lists the number of patients now living.

Table III records the results of treatment according to groups. We are tabulating on the basis of 1,001 patients who were traced out of a total of 1,094. In the small, operable group, 75 per cent of patients survived five years. Of the borderline cases, 61.53 per cent lived five years. The other two groups were larger: in the inoperable group, 21.49 per cent of the patients were living after five years; in the modified group, there were 24.82 per cent five-year survivals. The discrepancy between the results in the early and borderline groups, on the one hand, and the results in advanced cases on the other, emphasizes the necessity for early diagnosis. In the modified group, results have been slightly better than in the inoperable group. This table demonstrates, completely, the five-year results; the seven-

[1]Read at the Fifteenth Annual Meeting of the Radiological Society of North America, at Toronto, Canada, Dec. 2-6, 1929.

TABLE I

AGE INCIDENCE

Age, years	Modified group		Inoperable group		Borderline group		Operable group	
	Cases	Per cent	Cases	Per cent	Cases	Per cent	Cases	Per cent
20-24			1	0.16				
25-29	14	2.99	9	1.49				
30-34	55	11.75	25	4.15				
35-39	65	13.88	66	10.95	1	7.14	2	22.22
40-44	87	18.58	86	14.26	1	7.14	1	11.11
45-49	78	16.66	107	17.75	2	14.28	1	11.11
50-54	78	16.66	106	17.57	4	28.57	1	11.11
55-59	54	11.53	98	16.25	3	21.42	3	33.33
60-64	27	5.76	57	9.45	1	7.14		
65-69	7	1.49	36	5.97	1	7.14	1	11.11
70-74	3	0.64	9	1.49	1	7.14		
75-79			3	0.49				
Total	468		603		14		9	
Average age years	46.03	±0.29	50.37	±0.27	54.39	±1.62	50.84	±2.17

TABLE II

SURVIVORS OF ALL GROUPS BY YEARS

Year treated	Total cases	Years of life after treatment[2]													
		1916	1917	1918	1919	1920	1921	1922	1923	1924	1925	1926	1927	1928	1929
1915	5	1	1	1	1	1	1	1	1	1	1	1	1	1	1
1916	63		27	14	10	7	5	5	5	5	5	5	5	5	5
1917	93			51	28	21	18	17	14	13	11	10	9	8	6
1918	135				61	39	28	22	19	17	13	11	9	9	7
1919	145					77	44	32	21	20	18	18	15	15	10
1920	151						85	61	43	38	37	32	28	27	16
1921	118							64	52	46	40	40	36	35	20
1922	136								74	53	40	31	29	25	16
1923	135									83	60	51	43	42	27
1924	113										61	39	36	31	29

[2]The figures enclosed in black lines indicate the numbers of patients living five years after treatment.

year and ten-year results are necessarily fragmentary.

In Table IV we have summed up the five-year cures by groups. All 1,094 cases, considered together, show 21.84 per cent of five-year cures. Dropping out the modified group, the figure declines very slightly to 21.08 per cent. The operable and borderline five-year cures combined reach 60.86 per cent. But if just the traced cases are considered, 1,001 in all, our figures are higher, since, when we considered the 1,094 cases, we regarded all untraced patients as having died and we did not record them beyond the dates of their last examinations or letters. Thus, the percentages of five-year cures rise to 23.87, 23.15, and 66.66, respectively, and these percentages are more

TABLE III

RESULTS OF TREATMENT BY GROUPS

Group	Year	Total cases	Patients traced	Lived 3 years		Lived 5 years		Lived 7 years		Lived 10 years	
				Cases	Per cent	Cases	Per cent	Cases	Per cent	Cases	Per cent
Modified	1915	4	4	1	25.00	1	25.00	1	25.00	1	25.00
	1916	39	38	8	21.05	4	10.52	4	10.52	4	10.52
	1917	55	53	17	32.07	15	28.30	12	22.64	8	15.09
	1918	69	62	16	25.80	10	16.12	7	11.29	4	6.45
	1919	59	55	14	25.45	12	21.81	10	18.18	7	12.79
	1920	60	53	21	39.62	19	35.84	15	28.30		
	1921	36	33	10	30.30	9	27.27	7	21.21		
	1922	59	56	16	28.57	13	23.21	8	14.28		
	1923	48	44	18	40.90	15	34.09				
	1924	39	33	10	30.30	9	27.27				
	Total	468	431	131	30.39	107	24.82	64	14.84	24	5.56
Inoperable	1915	1	1								
	1916	24	24	2	8.33	1	4.16	1	4.16	1	4.16
	1917	38	34	4	11.76	2	5.88	1	2.94	1	2.94
	1918	65	60	11	18.33	8	13.33	5	8.33	4	6.66
	1919	85	80	18	22.50	8	10.00	8	10.00	3	3.75
	1920	89	80	21	26.25	17	21.25	12	15.00	1	11.11
	1921	74	68	31	45.58	26	38.23	23	33.82		
	1922	76	68	23	33.82	15	22.05	8	11.76		
	1923	85	81	32	39.50	26	32.09				
	1924	66	53	21	39.62	15	28.30				
	Total	603	549	163	29.69	118	21.49	58	10.56	10	1.63
Borderline	1918	1	1	1	100.00	1	100.00	1	100.00	1	100.00
	1919	1	1								
	1921	8	8	5	62.50	5	62.50	5	62.50		
	1922	1	1	1	100.00	1	100.00				
	1923	2	2	1	50.00	1	50.00				
	1924	1									
	Total	14	13	8	61.53	8	61.53	6	46.15	1	7.69
Operable	1920	2	1	1	50.00	1	50.00	1	50.00	1	50.00
	1924	7	7	5	71.42	5	71.42				
	Total	9	8	6	75.00	6	75.00	1	12.50	1	12.50
Grand total		1094	1001	(91.50 per cent)							

TABLE IV

FIVE-YEAR CURES BY GROUPS

Group	Cases	5-year cures, number	Per cent	Patients traced	5-year cures, number	Per cent
Operable, inoperable, borderline, and modified	1094	239	21.84	1001	239	23.87
Operable, inoperable, and borderline	626	132	21.08	570	132	23.15
Operable and borderline	23	14	60.86	21	14	66.66

nearly correct, as many untraced patients are probably still living.

Table V records the length of life in connection with the pathologic nature of the lesion. In one of the nine operable cases, no microscopic examination of the lesion was

TABLE V

CLASSIFICATION OF LENGTH OF LIFE BY GRADE OF PATHOLOGIC CHANGE

Group	Microscopic diagnosis	Cases	Impossible to be traced	Died within 1 year	Died, time not stated	Length of life, years					
						3	5	6	7	9	10
Modified	Epithelioma, not graded	28	4	5	3	14	12	12	9	8	7
	Epithelioma, graded 2	31	2	6	4	10	9	6	5	4	4
	Epithelioma, graded 3	104	6	21	13	39	28	18	14	7	4
	Epithelioma, graded 4	73	5	20	10	19	15	12	10	4	3
	Adenocarcinoma, not graded	6	2	1		4	3	3	3	2	2
	Adenocarcinoma, graded 1	3				2	2	2	1	1	
	Adenocarcinoma, graded 2	11		1		5	5	4	3	1	1
	Adenocarcinoma, graded 3	5				4	4	4	3	1	1
	Adenocarcinoma, graded 4	1				1	1	1	1		
	Adenocarcinoma and epithelioma, graded 2	1									
	Adenocarcinoma and epithelioma, graded 3	4		2		1	1				
	Total	267	19	56	30	99	80	62	49	28	22
	No biopsy	201	17	78	21	32	27	17	15	7	2
	Grand total	468	36	134	51	131	107	79	64	35	24
Inoperable	Epithelioma, not graded	14	2	4		2	1				
	Epithelioma, graded 2	35	3	11	4	11	7	5	4	1	
	Epithelioma, graded 3	166	17	39	18	51	43	33	22	4	1
	Epithelioma, graded 4	107	12	30	9	40	28	14	10	3	1
	Adenocarcinoma, not graded	3	1			2	2	1	1	1	1
	Adenocarcinoma, graded 1	1									
	Adenocarcinoma, graded 2	10		1	2	6	4	2	2	1	
	Adenocarcinoma, graded 3	3		1							
	Adenocarcinoma, graded 4	1		1							
	Adenocarcinoma and epithelioma, graded 2	1				1	1	1			
	Adenocarcinoma and epithelioma, graded 3	1				1					
	Total	342	34	87	33	114	86	56	39	9	3
	No biopsy	261	20	95	26	49	32	24	19	14	7
	Grand total	603	54	182	59	163	118	80	58	23	10
Borderline	Epithelioma, not graded	1	1								
	Epithelioma, graded 3	5			1	3	3	3	3		
	Epithelioma, graded 4	2				2	2	2			
	Total	8	1		1	5	5	5	3		
	No biopsy	6		2		3	3	3	3	1	1
	Grand total	14	1	2	1	8	8	8	6	1	1
Operable	Epithelioma, not graded	3				3	3				
	Epithelioma, graded 2	1				1	1				
	Epithelioma, graded 3	3	2			1	1				
	Epithelioma, graded 4	1		1							
	Total	8	2	1		5	5				
	No biopsy	1				1	1	1	1	1	1
	Grand total	9	2	1		6	6	1	1	1	1

made; likewise, this confirmatory measure was not employed in six of fourteen borderline cases, in 261 of 603 inoperable cases, and in 201 of 468 modified cases. Biopsy is not essential to diagnosis; nevertheless, of late years we usually take tissue to allow of correlation of results with the histologic pathology. In modified cases there fre-

TABLE VI

THREE-YEAR AND FIVE-YEAR CURES BY GRADE OF PATHOLOGIC CHANGE

Group	Microscopic diagnosis	Total cases	Patients traced	Lived 3 years	Per cent	Lived 5 years	Per cent
Modified	Epithelioma, graded 2	31	29	10	34.48	9	31.03
	Epithelioma, graded 3 and 4	177	166	58	34.94	43	25.90
	Adenocarcinoma, graded 1 and 2	14	14	7	50.00	7	50.00
	Adenocarcinoma, graded 3 and 4	6	6	5	83.33	5	83.33
Inoperable	Epithelioma, graded 2	35	32	11	34.37	7	21.87
	Epithelioma, graded 3 and 4	273	244	91	37.29	71	29.09
	Adenocarcinoma, graded 1 and 2	11	11	6	54.54	4	36.36
	Adenocarcinoma, graded 3 and 4	4	4				
Borderline	Epithelioma, graded 3 and 4	7	7	5	71.42	5	71.42

quently is surface healing and to obtain tissue we would have to cut through barriers of protective tissue, which we dislike to do.

From Table V it appears that among the 625 cases in which microscopic examinations were made, in 574 (91.84 per cent) epitheliomas were found; in 44 (7.04 per cent) adenocarcinomas, and in seven (1.12 per cent) mixtures of the two. Further analysis shows that among all of these malignant lesions, 476 (76.16 per cent) were graded 3 or 4 according to Broders' classification; 94 lesions (15.04 per cent) were graded 1 or 2, and 55 lesions (8.80 per cent) were not graded.

Table VI gives the three-year and five-year cures by grade of malignancy.

A study of our mortality in hospital was made. Our treatment extends over a period of three or more weeks and the patients are watched carefully for complications. Complications develop in a few patients each year; we encounter hemorrhage, pelvic cellulitis, pyometritis, peritonitis, and so forth. Treatment is halted at once at the outset of any of these accidents and is either abandoned or cautiously continued, as the outcome warrants. During the decade reviewed, mortality in hospital has been very low: five cases (1.06 per cent) in the modified group of 468 cases and six cases (0.99 per cent) in the inoperable group of 603 cases. None of the patients in the operable and borderline groups died.

SUMMARY

We have reviewed the cases of carcinoma of the cervix treated with radium at The Mayo Clinic during the years 1915 to 1924, inclusive, and have epitomized the results of treatment. The total number of patients treated was 1,094; of these, 1,001 (91.50 per cent) have been traced. We have divided the total into four groups: operable, borderline, inoperable, and modified. Of the traced cases, our five-year cures compose 75 per cent of the operable group, 61.53 per cent of the borderline, 21.49 per cent of the inoperable, and 24.82 per cent of the modified. Of the 625 cases (57 per cent of all cases) in which microscopic examinations of the growths were performed, epitheliomas were found in 574 (91.84 per cent), adenocarcinomas in 44 (7.04 per cent), and mixtures of the two in seven (1.12 per cent). Lesions graded 3 and 4 totaled 476 cases (76.16 per cent); 94 (15.04 per cent) were of grades 1 and 2, and 55 (8.80 per cent) were not graded. In this series, patients with adenocarcinoma (of all four grades) appear to have had a better rate of survival than those with epithelioma. Patients with epithelioma graded 3 and 4 had

a slightly better rate of survival than those with epithelioma graded 2, except for the results after five years among the modified cases. Finally, the rate of mortality in hospital was 1.06 per cent among the modified cases, 0.99 per cent for the inoperable group, and zero for the operable and borderline groups.

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CARCINOMA OF THE CERVIX[1]

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RADIATION therapy for the treatment of malignant disease of the cervix was established at the Memorial Hospital in 1915, under the direction of Dr. Harold Bailey. During the past fifteen years about two thousand cases of carcinoma of the cervix have been under observation.

The principle of cross-firing the lesion from multiple foci was instituted by Bailey, and he was one of the first gynecologists to attack cancer of the cervix by the routine application of radiation externally around the pelvis as well as by means of vaginal applicators, intracervical capsules, and interstitial radiation by needles or seeds.

During the first seven years, from 1915 to 1921, under Bailey's direction, radium was the only source of radiation employed.

From January, 1922, to date, under the writer's supervision, the use of radium as the source of external radiation has been omitted and the roentgen ray has been substituted for it. This change in routine was first forced upon us because of the large number of patients applying for treatment. The cervix cases were requiring so much radium in the pack and in vaginal applicators that the supply for other cases was inadequate, or frequently could not be obtained at all.

After consultation with Dr. G. Failla, of the Department of Physics, it was determined that insofar as percentage of skin erythema dose was concerned at a point in the pelvis 10 cm. below the surface, we could obtain a greater percentage even with the low voltage X-ray machine in use at that time than was being obtained with the small radium block then in use for external application. Moreover, from the standpoint of economy in time of treatment and cost to patient there was a decided advantage in favor of the roentgen ray.

The plan of treatment followed for the past eight years, therefore, has consisted of a combination of radium at the site of the primary lesion and X-ray applied through multiple foci about the pelvic girdle. The thought underlying this is the desire to irradiate, as intensively as possible, both the lesion and the lymphatic drainage area about it, in order to control not only the primary disease but also the inevitable parametrial metastasis.

Since at least two-thirds of all cases already have parametrial involvement when first seen, it would seem highly desirable to attempt at least to inhibit the growth activity in these areas, even if the disease is too extensive to be cured. During the past three or four years high voltage X-ray has replaced low voltage; as a result we estimate that approximately 38 per cent of a skin erythema dose is obtained 10 cm. below the surface from a single exposure.

Figure 1 indicates in diagrammatic form the varying amounts of radiation obtained from high voltage X-ray in different portions of the pelvis measured in skin erythema doses. The factors are 200 K.V., ½ mm. copper, 1 mm. aluminum, 50 cm. target skin distance, 4 milliamperes, 60–80 minutes treatment, 15 × 15 cm. field.

This diagram indicates that a minimum of 100 per cent and a maximum of 120 per cent of a skin erythema dose is distributed throughout the greater portion of the pelvis, extending from the middle of the acetabulum on one side to the corresponding place in the opposite side. The high percentage indicated from the cervix to the sacrum

[1]Read before the Radiological Society of North America at the Fifteenth Annual Meeting, at Toronto, Dec. 2–6, 1929.

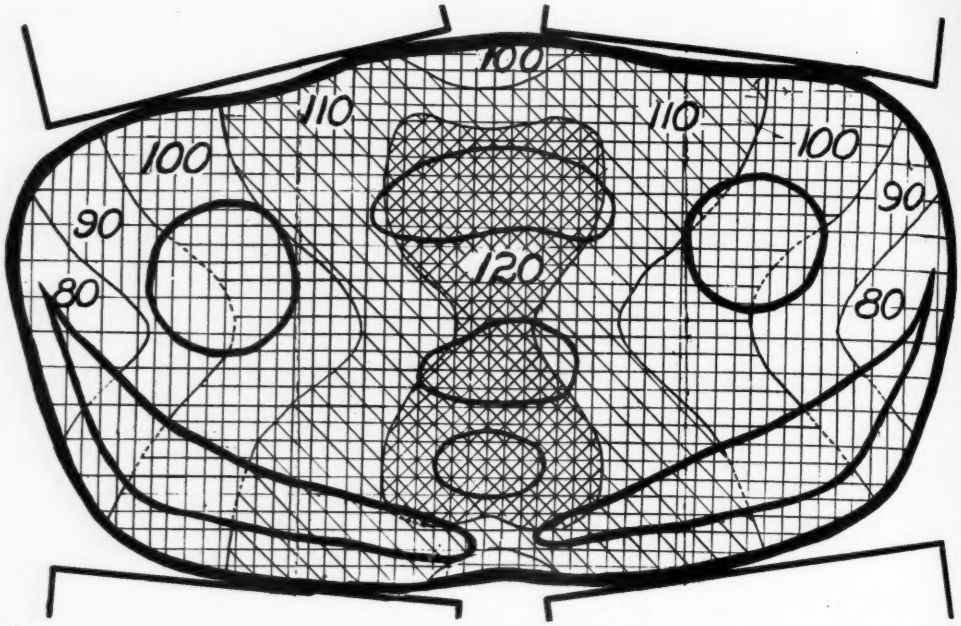

Fig. 1. Distribution of radiation in medium-sized female pelvis when irradiated with high voltage X-rays through four portals, as shown: 200 K.V., 0.5 mm. copper and 2.5 mm. aluminum filter, 50 cm. target-skin distance, 15×15 cm. fields, 1 erythema dose for each portal.

would seem to be quite important. This area includes a segment of the parametrium embracing the uterosacral ligaments, the perirectal area, and the retroperitoneal lymphatic glands anterior to the sacrum. Lesions in the posterior half of the cervix are prone to send off early metastases to this area and although the lesion may seem to be an early one, the case may do badly. Of course, it is to be realized that these figures refer only to the percentage of radiation obtained with the high voltage X-ray cycle and do not include the value represented by the radium applications.

Those figures may be to some extent appreciated from a study of Figure 2 and the accompanying tables. The figures given therein include the total value of the combined radiation with radium and X-ray, as applied by us, at different points, with relation to the source of radiation. While these values are all approximate, it is interesting to note that the lowest value indicated is 335 per cent of a skin erythema dose and is obtained 5 cm. from the capsule in the cervix. Also, of the total radiation received at this point (15) 30 per cent is attributable to X-ray, whereas Point 2, 1 cm. distant from the cervical capsule, receives 5,690 per cent of a skin erythema dose, of which only 2 per cent is of X-ray origin and 98 per cent is derived from radium.

A study of Figures 1 and 2 and the tables accompanying the latter enables us to appreciate the relative as well as the actual values of different methods of application of radiation therapy. They also indicate the heavy radiation obtained by cross-firing from several foci and the great ease with which the total dosage in any given area can be enormously increased by the use of interstitial radiation with needles or filtered implants, such as gold or platinum seeds.

We are of the opinion that the large number of advanced cases constantly seen, because of the difficulties of early diagnosis, makes it extremely improbable that we shall obtain more than 40 to 50 per cent of five-

year cures by radiation or surgery, singly or combined, in the favorable cases. By favorable cases we mean the so-called clinically early and borderline groups.

per cent with this operation, as against a mortality of 1½ to 2 per cent from radiation therapy. Moreover, there are very few surgeons who can hope to achieve the high

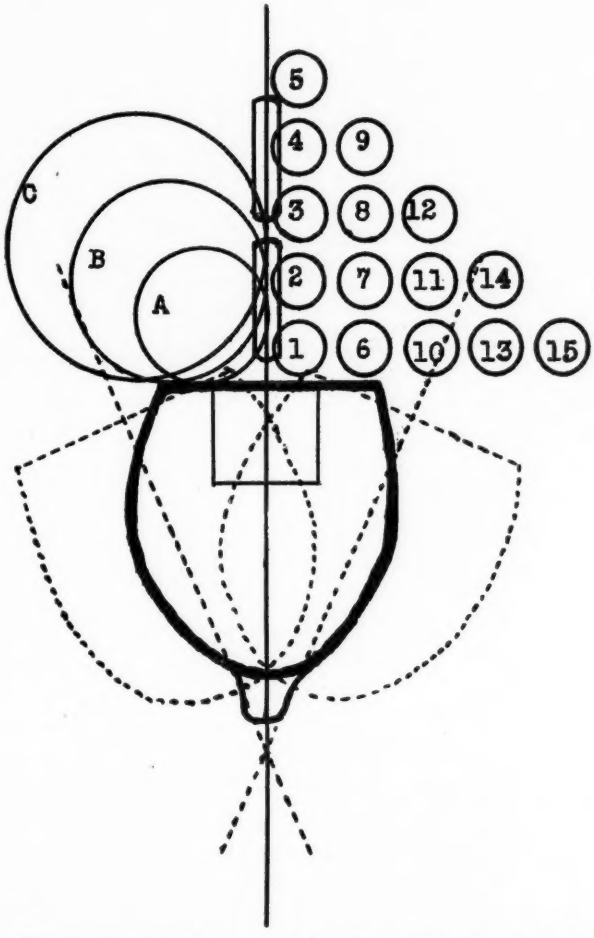

Fig. 2. Bomb and cervix tandem in position (actual size). See Table I for doses delivered at numbered points, also for millicuries in gold seeds necessary to deliver 100, 500, and 1,000 per cent erythema dose throughout lettered spheres. One thousand millicurie-hours from bomb in each position; one thousand millicurie-hours from upper tube of tandem; two thousand millicurie-hours from lower tube of tandem.

When we speak of surgery as giving such a high percentage of five-year cures we refer to the radical Wertheim operation, and one must not, of course, overlook the high associated primary mortality of about 15 to 20 percentage of cures referred to with hysterectomy, whereas practically all specialists of experience in radiation therapy seem to obtain about 40 to 50 per cent of five-year cures.

Unfortunately five-year freedom from recurrence does not always mean a cure. Recurrences are seen in the parametrial lymph glands in the sixth, seventh, and eighth year after treatment. Local recurrences in the cervix after the fifth year are, however, quite unusual.

In all instances in which the disease is too advanced to attempt other than palliation of symptoms, chief reliance is placed on high voltage X-ray treatment. The cycle may be repeated two or three times at intervals of six weeks. If the lesion seems to be radiosensitive in its response to the X-ray, occasionally vaginal applications of radium are then also given.

Our routine procedure in favorable cases has been radium first, followed promptly by X-ray; the latter cycle is repeated once or twice at intervals of six to eight weeks after the first cycle. The cycle now consists of five exposures, four of which include the entire circumference of the pelvic girdle, the fifth being centered posteriorly over the spine of the third lumbar vertebra and is given for its effect upon the prevertebral lymph glands in this area.

Postmortem investigations in patients who have died with carcinoma of the cervix have revealed extensive involvement of the retroperitoneal glands anterior to the lumbar spine. This involvement has seemed to be largely responsible for the persistent and very severe pain which these patients suffer for months before death. We are hopeful that by adding this lumbar exposure to the full pelvic cycle something of value will be gained for the patient.

Numerous writers have reviewed the histology of their cases of cervical cancer, and there seems to be a consensus of opinion upon certain points.

First, the lesions are almost exclusively of the squamous epidermoid variety, with a very small number of adenocarcinomata—not over 3 to 6 per cent—which arise from the cells in the cervical glands.

Second, the squamous epidermoid variety can be readily divided into three large histologic groups according to variations in cellular structure and characteristics. Various names have been given to these groups by different writers, but there is no diversity of opinion on the histologic criteria of the individual groups.

Briefly, Group 1 (adult, spinal, ripe) is composed of tumors in which the predominant cell type is a fully developed, mature, adult squamous cell, with more or less tendency to pearl formation. The cells and nuclei resemble each other and have similar staining qualities. These cases comprise about 20 per cent of the total. Group 2 (plexiform, transitional, midripe) consists of cases in which the histologic appearance is changing from that of a mature cell to one that is less mature, and the cells vary more in size and staining qualities. Mitoses are more in evidence and in the majority of cases the histologic picture suggests a pattern or architectural structure of plexiform type. This is the largest group and includes about 60 per cent of the cases.

The third group (anaplastic, spindle, unripe, embryonal), as the various names given it imply, consists of tumors in which the histologic structure is that of a rapidly growing lesion made up of small cells, immature, with many mitoses, marked variation in staining qualities, relatively little stroma, and a tendency to invade lymphatics early. This group comprises about 20 per cent of the whole.

These percentages vary, but always about four-fifths of the lesions (80 per cent) are in the second and third groups. It is recognized that the cell most resistant to radiation in the three groups is the spinal, or fully developed adult type of squamous cell—that one which typifies Group 1 and represents only one-fifth (20 per cent) of our total lesions. We believe it is reasonable to assume that the high proportion of relatively radio-

sensitive lesions in the second and third histologic groups of cervix cancer accounts for the satisfactory response which so many of these cases make to radiation therapy, even when they are moderately advanced clinically.

We also wish again to emphasize, as other writers have done, that the most important factor in prognosis, regardless of the method of treatment employed or the histologic structure, is early diagnosis.

Since about 60 per cent of the cases are clinically unfavorable when recognized and as a rule appear with a large, infected, ulcerated lesion in the cervix, we have recently changed our routine treatment and all such cases receive X-ray treatment before the radium is given. In addition, they are instructed to take copious, warm antiseptic vaginal douches. Cases thus treated usually show marked improvement in the appearance of the primary lesion in ten days. It is then possible to apply radium to better advantage and with much less risk of a complicating pelvic infection.

Moreover, since September, 1928, we have omitted interstitial application of radium with needles or seeds from the first series of treatments. They are reserved for use three or more weeks after the primary series of treatments with X-ray and radium has been finished.

At that time any portion of the primary lesion which does not seem to be regressing satisfactorily can be treated to advantage with needles or seeds and with much less risk of infection or of an overdosage which may lead to the formation of fistulæ, or of spreading the disease by puncture, as the vitality of the cancer cells has been damaged by the preceding treatments.

It is interesting to note that we have found it necessary to use interstitial or buried radiation as a routine part of the after-treatment in only a rather small percentage of the cases.

TABLE I.—RADIATION DOSES DELIVERED BY CERVIX APPLICATORS AT POINTS INDICATED ON DIAGRAM (FIG. 2)

Bomb: 1,000 mc.-hr. in each position.
Tandem: 1,000 mc.-hr. from upper tube.
2,000 mc.-hr. from lower tube.
X-rays: 1 high voltage cycle, assumed to deliver 100 per cent erythema dose at each point within the area considered.

Point	Applicator	Per cent S.E.D.	Per cent S.E.D.	Per cent Total	Per cent Total
1	Bomb left	25		1	
	center	210	270	10	13
	right	35		2	
	Tandem upper	90	1690	4	82
	lower	1600		78	
	X-rays	100	100	5	5
	Total	2060	2060	100	100
2	Bomb left	20		—	
	center	100	150	2	2
	right	30		—	
	Tandem upper	140	5440	2	96
	lower	5300		94	
	X-rays	100	100	2	2
	Total	5690	5690	100	100
3	Bomb left	15		1	
	center	55	90	4	6
	right	20		1	
	Tandem upper	790	1320	53	88
	lower	530		35	
	X-rays	100	100	6	6
	Total	1510	1510	100	100
4	Bomb left	10		—	
	center	35	65	1	2
	right	20		1	
	Tandem upper	3140	3420	88	95
	lower	280		7	
	X-rays	100	100	3	3
	Total	3585	3585	100	100
5	Bomb left	10		2	
	center	25	50	4	9
	right	15		3	
	Tandem upper	310	440	53	75
	lower	130		22	
	X-rays	100	100	16	16
	Total	590	590	100	100
6	Bomb left	15		1	
	center	50	125	5	12
	right	60		6	
	Tandem upper	100	810	10	78
	lower	710		68	
	X-rays	100	100	10	10
	Total	1035	1035	100	100
7	Bomb left	15		1	
	center	55	120	5	10
	right	50		4	
	Tandem upper	120	980	10	82
	lower	860		72	
	X-rays	100	100	8	8
	Total	1205	1205	100	100

(Continued on next page)

(Table 1, continued)

Point	Applicator	Per cent S.E.D.	Per cent S.E.D.	Per cent Total	Per cent Total
8	Bomb left	5		—	
	center	40	80	4	8
	right	35		4	
	Tandem upper	340	790	35	80
	lower	450		45	
	X-rays	100	100	12	12
	Total	970	970	100	100
9	Bomb left	10		1	
	center	30	70	4	9
	right	30		4	
	Tandem upper	460	700	52	80
	lower	240		28	
	X-rays	100	100	11	11
	Total	870	870	100	100
10	Bomb left	10		1	
	center	25	175	3	23
	right	140		19	
	Tandem upper	90	460	12	62
	lower	370		50	
	X-rays	100	100	15	15
	Total	735	735	100	100
11	Bomb left	10		1	
	center	30	115	4	15
	right	75		10	
	Tandem upper	130	500	18	70
	lower	370		52	
	X-rays	100	100	15	15
	Total	715	715	100	100
12	Bomb left	10		2	
	center	30	85	5	14
	right	45		7	
	Tandem upper	185	425	30	70
	lower	240		40	
	X-rays	100	100	16	16
	Total	610	610	100	100
13	Bomb left	10		2	
	center	15	110	3	22
	right	85		17	
	Tandem upper	60	285	12	58
	lower	225		46	
	X-rays	100	100	20	20
	Total	495	495	100	100
14	Bomb left	5		1	
	center	15	75	3	15
	right	55		11	
	Tandem upper	85	310	18	64
	lower	225		46	
	X-rays	100	100	21	21
	Total	485	485	100	100
15	Bomb left	5		1	
	center	10	60	3	17
	right	45		13	
	Tandem upper	45	175	13	53
	lower	130		40	
	X-rays	100	100	30	30
	Total	335	335	100	100

TABLE II.—GOLD SEEDS NECESSARY TO DELIVER SPECIFIED DOSES IN GIVEN SPHERES

Sphere	Diam. cm.	Gold Seeds for 100 Per Cent S.E.D. mc.	Gold Seeds for 500 Per Cent S.E.D. mc.	Gold Seeds for 1,000 Per Cent S.E.D. mc.
A	2.0	1	5	10
B	3.0	2.2	11	22
C	4.0	4.4	22	44

Reviewing our cases treated with radium and low voltage X-ray in 1922, 1923, and 1924, and dividing them into two groups—*favorable* to include the early and borderline, and *unfavorable*, representing the advanced cases—there are 44.5 per cent of five-year clinical cures in the favorable group. This percentage will vary somewhat from year to year, but on the whole is fairly stationary and corresponds closely with other published reports in this country and in Europe.

I wish to express my thanks to Mrs. Edith Quimby, of the Department of Physics, who drew the diagrams and constructed the tables, and to Dr. Charles Lucas for his careful review of the records of 1922, 1923, and 1924.

HISTOLOGICAL STRUCTURE, CLINICAL GROUPING, AND PROGNOSIS OF CANCER OF THE UTERINE CERVIX AND THE BREAST[1]

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MANY of the most important facts about the prognosis of tumors can be learned only by the earnest cooperation of the surgeon, the radiologist, and the pathologist. The microscope determines the finer structure of the tumor, and enables it to be classified. From a certain type of structure, a certain behavior of growth may be predicted. But confirmation or refutation of the pathologist's prognosis must be verified from a study of the clinical course of the tumor. The pathologist sees only the tissue, the surgeon and radiologist observe the patient and thus know the eventual end-result. The clinician's most important contribution to medical science will be the publication of his final results. In carcinomata treated by surgery or radiology the questions to be studied are: Did a recurrence of the growth ensue? Was the recurrence due to the nature of the growth, or the inadequacy of the operation or radiation treatment or the dissemination of the cancerous disease?

It seems safe to say that if a tumor be completely removed by surgery it cannot and will not recur. Recurrences are, therefore, due to incomplete removal—a portion of the original tumor was left behind. If fringes of the tumor remain, it is equivalent to leaving some of the original tumor; if during operation some of the tumor cells be scattered over the wound, recurrences take place from their growth; if metastasis to regional lymph nodes or to viscera has taken place, the tumor continues to grow. The entire history of the primary, recurrent or secondary growths is, therefore, of one tumor substance, localized or distributed. Surgery, to be successful, must eradicate the entire tumor-bearing area.

Since the advent of radiology in the treatment of carcinoma clinical observations have had to be added concerning the study of the action of rays, the technic of the application of rays, and the end-results. Radiations act (1) by restraint of cell division without complete destruction of cell function; (2) by reactivation of the cell to mature from its undifferentiated condition to that state where the inhibitions or restraints of growth gradients are once more effective, and (3) by direct cell destruction. If radiations act homogeneously on the entire cell masses so that tumor cell division and differentiation become normal or cell destruction is complete, then the growth will not recur. Should the radiosensitivity of the tumor cell be of a low degree or the radiations be applied faultily, then recurrences will take place, just as incomplete surgical removal will cause continuation of the growth.

In recent years numerous reports have appeared in the medical literature dealing with investigations into the correlations existing between the histological structure, the clinical extent of the growth, the surgical and radiological treatment, and the prognosis of malignant tumors. The most reliable information in regard to the prognosis of malignant tumors is at present obtained by an evaluation of the histological structure and a consideration of the clinical extent. These

[1]Read before the Radiological Society of North America at the Fifteenth Annual Meeting, at Toronto, Dec. 2–6, 1929.

two factors have been taken into account in the work presented in this paper.

THE HISTOLOGICAL MALIGNANCY

For the determination of the histological malignancy twenty factors characterizing the degree of differentiation and anaplasia of the tumor parenchyma and the antiblastic condition of the stroma were evaluated according to the method elaborated by one of us (Hueper). The list of these factors composing the "histological malignogram" (Hueper) and showing the numerical values given is as follows:

I.	Special cellular and structural characteristics of carcinoma			Valued 5–20
	1. Special cell type of carcinoma	valued	1–4	
	2. Nucleo-cytoplasmic coefficient	"	1–4	
	3. Number of "pencil-cells"	"	1–4	
	4. Infiltrative growth of carcinoma	"	1–4	
	5. General type of carcinoma (parenchyma-stroma relation)	"	1–4	
II.	Characteristics of cytoplasm			Valued 5–20
	6. Irregularity in size of cells	"	1–4	
	7. Irregularity in shape of cells	"	1–4	
	8. Distinctness in outline of cells	"	1–4	
	9. Chromatism of cytoplasm	"	1–4	
	10. Functional activity of cells	"	1–4	
III.	Characteristics of nuclei			Valued 6–24
	11. Irregularity in size of nuclei	"	1–4	
	12. Irregularity in shape of nuclei	"	1–4	
	13. Chromatism of nuclei	"	1–4	
	14. Hyperchromatism of nuclei	"	1–4	
	15. Number of mitoses and prophases	"	1–4	
	16. Irregularity of mitoses	"	1–4	
IV.	Characteristics of stroma			Valued 4–16
	17. Character of stroma	"	1–4	
	18. Vascularity of stroma	"	1–4	
	19. Type of cellular infiltration	"	1–4	
	20. Amount of cellular infiltration	"	1–4	

DEFINITIONS OF FACTORS AND TECHNIC OF EVALUATION

1. *Special cell type of carcinoma.* After a general classification of the carcinomata into two main groups, the primary solid carcinomata and the glandular or adenocarcinomata, the tumors are subdivided into four subgroups according to their general structure and the maturity of the predominant cell type. Carcinomata of Sub-group 1 are evaluated with 1 point, those of Sub-group 2 with 2 points, those of Sub-group 3 with 3 points, and those of Sub-group 4 with 4 points.

A. Glandular carcinomata
   1. Malignant adenoma
   2. Papillary and gelatinous adenocarcinoma
   3. Adenocarcinoma simplex
   4. Solid adenocarcinoma

B. Primary solid carcinoma
   1. Spinous-cell carcinoma, with cornifications
   2. Spinous-cell carcinoma, without cornifications
   3. Round-cell carcinoma
   4. Spindle-cell carcinoma

2. *Nucleo-cytoplasmic coefficient.* The relative number of those carcinoma cells which show a large nucleus surrounded by a small amount of cytoplasm is estimated. If 10 per cent or less of such cells are found among the tumor cells, 1 point is counted. Their presence in from 10–20 per cent is evaluated with 2 points, in from 20–30 per cent with 3 points, and in more than 30 per cent with 4 points.

3. *Number of "pencil-cells."* "Pencil-cells," which are slender cells with dark stained nuclei invading and destroying the carcinoma cells, are counted with 1 point when they are very numerous. Two points

are evaluated when they are present in moderate number, 3 points when they are scanty, and 4 points when they are completely absent.

4. *Infiltrative growth of cells.* The presence of well defined outlines in the majority of the carcinomatous cell nests is evaluated with 1 point, diffuse invasion present in from 25–50 per cent of the cell strands with 2 points, in from 50–75 per cent with 3 points, and in more than 75 per cent with 4 points.

5. *General type of carcinoma.* If 75 per cent or more of the carcinoma is composed of parenchyma and 25 per cent or less of stroma, 4 points are counted; if from 50–75 per cent is parenchyma and from 25–50 per cent is stroma, 3 points are evaluated; if from 25–50 per cent is parenchyma and from 50–75 per cent is stroma, 2 points are noted, and if 25 per cent or less is parenchyma and 75 per cent or more is stroma, 1 point is counted.

6 and 7. *Irregularity in size and shape of cells.* The average size and shape of the tumor cells are studied. Deviations from this size and shape, respectively, in from 40–50 per cent of the cells are evaluated with 4 points, in from 30–40 per cent with 3 points, in from 20–30 per cent with 2 points, and in 20 per cent or less with 1 point.

8. *Distinctness in outline of cells.* Distinct outlines present in 75 per cent or more of the tumor cells are evaluated with 1 point, in from 50–75 per cent with 2 points, in from 25–50 per cent with 3 points, and in less than 25 per cent with 4 points.

9. *Chromatism of cytoplasm.* If the majority of the carcinoma cells have an almost unstained cytoplasm, while the connective tissue cells are distinctly pink stained, 4 points are counted. If the cytoplasm is only slightly pink stained, 3 points are evaluated; a moderately pink stained cytoplasm is counted 2 points and a distinctly pink stained cytoplasm 1 point.

10. *Functional activity of cells.* Granules of keratin and droplets of mucus, respectively, or the presence of vacuoles in tumor cells which do not show signs of degeneration, are regarded as evidence of functional activity. If these products are present in less than 10 per cent of the tumor cells, 4 points are evaluated; if they are seen in 10–20 per cent of the tumor cells, 3 points are counted; if present in 20–30 per cent, 2 points are noted, and if observed in more than 30 per cent of the cells, 4 points are marked.

11 and 12. *Irregularity in size and shape of the nuclei.* The same viewpoints and percentages are used in the evaluation of this factor as described for Factors Nos. 6 and 7.

13. *Chromatism of nuclei.* Four points are evaluated if the majority of the nuclei is almost as deeply stained as those of lymphocytes, 3 points if they are somewhat paler, 2 points if they are considerably paler, and 1 point if they are very pale compared with the nuclei of fibroblasts.

14. *Hyperchromatism of nuclei.* If 20 per cent or more of the nuclei are as dark as those of lymphocytes, the factor is evaluated with 4 points; if from 15–20 per cent are hyperchromatic, 3 points are counted; if from 10–15 per cent, 2 points, and if such nuclei are present in less than 10 per cent, 1 point is counted.

15. *Number of mitoses and prophases.* The mitotic figures and prophases in 10 fields are counted with the help of an oil immersion, giving a magnification of 1,050 times. Twenty or more mitoses and prophases receive 4 points, 15–19 are noted with 3 points, 10–14 with 2 points, and 0–9 with 1 point.

16. *Irregularity of mitoses.* Pathological types of mitoses present in less than 10 per cent of the mitotic figures are counted with 1 point, in from 10–20 per cent with 2 points, in from 20–30 per cent with 3 points, and in more than 30 per cent with 4 points.

17. *Character of stroma.* A very loose, edematous connective tissue stroma is count-

ed 4 points, a moderately loose one 3 points, a fibrous one 2 points, and a fibrous one with extensive hyalinizations 1 point.

18. *Vascularity of stroma.* A highly vascular stroma is evaluated with 4 points, a moderately vascular one with 3 points, a slightly vascular one with 2 points, and one with very scanty vessels with 1 point.

19. *Type of cellular infiltration of stroma.* A predominantly eosinophilic infiltration of the stroma is evaluated with 1 point, one mainly composed of lymphocytes mixed with some eosinophiles with 2 points, one consisting of lymphocytes, plasma cells, and scanty neutrophilic leukocytes with 3 points, and one predominantly composed of neutrophilic leukocytes with 4 points.

20. *Amount of cellular infiltration of stroma.* A dense infiltration of the stroma is evaluated with 1 point, a moderately dense one with 2 points, a slight one with 3 points, and a very scanty one with 4 points.

The numerical values obtained by this method are added and the sum resulting is called "histological malignancy index" (Hueper), which represents the numerical expression of the potential malignancy of a given tumor as evidenced by its histological structure. The numerical range of the "histological malignancy index" is between 20 and 80. The evaluations show that the malignancy increases with an increase in the value of the malignancy index.

THE DETERMINATION OF THE CLINICAL EXTENT OF THE GROWTH

The clinical extent, the second factor, which has an important effect upon the prognosis of malignant tumors, is represented in the clinical grouping of carcinomata of the uterine cervix and of the breast as elaborated by one of us (Schmitz). Its estimation is based on physical findings. The carcinomata are divided into primary, secondary, and recurrent. The factors which determine the clinical grading of the primary carcinomata of the uterine cervix are:

Group P1 signifies a cancer growth clearly localized within the cervix. It should be about 1 cm. in diameter. The size is determined by palpation and inspection. The genital organs are movable within normal limits.

Group P2 indicates a growth which has extended to the periphery of the cervix in a longitudinal or transverse direction. The uterus has an impeded movability due to a dough-like consistency and decreased elasticity of the paracervical tissues.

Group P3 means that either one or both parametria or the regional lymph nodes have been invaded, a fact which is elicited by rectal examination. The tumor mass is movable, though elasticity of the tissues is lost.

Group P4 includes the carcinomata with absolute fixation, vaginal, vesical, or rectal extension, distant secondary growths, advanced cachexia.

The primary carcinomata of the breast are classified according to similar considerations:

Group P1 represents a clearly localized, freely movable growth which is not adherent to skin or pectoral fascia and which has not produced any metastases in the regional lymph nodes, as evidenced by pre-operative palpation and corroborated by post-operative histological examination.

Group P2 signifies a single node which is still freely movable but which has produced metastases either in the breast or lower axillary lymph nodes, and primary multiple tumors as observed after chronic cystic mastitis.

Group P3 includes those tumors which have become adherent to the skin or fascia or both. There may be multiplicity in the breast and metastases in the lower and up-

per axillary lymph nodes. The primary and metastatic tumors are movable, though movability is impeded.

Group P4 means that the tumor has either permeated the entire skin with ulceration, or has become fixed to the chest wall, or has produced fixed metastases in the upper axillary lymph nodes, or has invaded the supraclavicular lymph nodes, or caused multiple invasions of the skin. The other breast also may be involved. Metastases may have been produced in distant organs. The primary and metastatic growths are firmly fixed to the skin or chest wall or axillary structures.

The characteristics of the groups in the recurrent carcinomata are: Group R1 contains the local but freely movable, clearly localized recurrences; Group R2 the regional, freely movable recurrences; Group R3 the local and regional movable recurrences, and Group R4 the local or regional recurrences, with fixation or secondary invasion in distant organs (supraclavicular lymph node, bone, etc.).

The clinical grouping has a threefold purpose. It indicates those cases which invariably have a poor prognosis (Group 4). It furnishes, furthermore, the correct indications for treatment and is an aid in establishing exact statistics to determine the therapeutic efficacy of either operation or radiation. Table I comprises the cases of primary carcinomata of the cervix and the breast admitted and treated up to the end of 1924 in the clinic of Schmitz.

RESULTS OF STUDY

Malignancy indices were determined from 225 cases of carcinoma of the uterine cervix and 136 cases of carcinoma of the breast. The patients entered Mercy Hospital in the years 1922–1926.

MALIGNANCY INDEX AND END-RESULTS

The prognostic value of the histological malignancy index was tested against the end-results obtained. The malignancy indices were first determined and they then were entered in the clinical histories. Thus the work of the pathologist could not be influenced by the end-results obtained. The following classification of the end-results was made:

Clinical End-result 1 means that the patient was free from symptoms and showed anatomical healing three years after termination of the treatment.

End-result 2 indicates death during the third year.

End-result 3 means death during the second year.

End-result 4, death during the first year after treatment. Cases of Clinical Group 4 are eliminated from the following compilation as they almost always have a poor prognosis, regardless of the histological malignancy index and the treatment used. The end-results were known in 100 cases of cervical carcinoma and 71 cases of carcinoma of the breast.

To test the histological malignancy index

TABLE I

FIVE-YEAR GOOD END-RESULTS IN PRIMARY CARCINOMATA

Group	CERVIX			BREAST		
	Number	Well	Per cent	Number	Well	Per cent
P 1	23	18	78.27	13	9	69.23
P 2	48	20	41.68	29	15	51.72
P 3	161	20	12.42	34	4	11.77
P 4	100	0	0	31	1	3.23
Total	332	58	17.50	107	29	27.10

Operability, *i.e.*, Groups 1 and 2, is 21.09 per cent. Relative curability in 71 operable cases was 38, or 53.52 per cent, with the use of radium and X-rays.

Operability, *i.e.*, Groups 1 and 2, is 39.25 per cent. Relative curability in 42 operable cases was 24, or 50.72 per cent, with operation and post-operative X-ray.

against the good End-results 1 the values were divided into four even parts. The average malignancy index value of cervix carcinomata is 55.76 and for breast carcinomata 56.04; hence 56 was taken as the average value. Each malignancy index group has a range of 12 points, that is: Group 1, from 32 to 44; Group 2, from 45 to 56; Group 3, from 57 to 68, and Group 4, from 69 to 80.

TABLE III

AVERAGE MALIGNANCY INDEX

	Cervix	Breast
End-result 1	52.45	54.48
End-result 2	53.00	59.11
End-result 3	60.00	58.70
End-result 4	61.00	61.35

It is evident from Table IV (page 229) that carcinomata of the breast have on the average a somewhat higher histological malignancy than those of the uterine cervix, as carcinomata of the breast are less frequent than those of the cervix in the first two malignancy groups.

TABLE II

	Breast	Cervix	Breast	Cervix	Breast	Cervix	Breast	Cervix
Malignancy Index	32–44		45–56		57–68		69–80	
Number of cases	2	5	24	28	24	27	3	2
Number of End-result 1	2	4	16	17	9	7	0	0
Percentage of End-result 1	100	80	66	50.7	37.5	25.8	0	0

The practical significance of the histological malignancy index is strikingly demonstrated by the agreement of the figures given above. The general average malignancy index of the 136 breast carcinomata is 56.04 and that of the 225 carcinomata of the uterine cervix is 55.76. The average malignancy index of 28 breast carcinomata with End-result 1 is 54.48 (range 40–64) and of 31 cervical carcinomata 52.45 (range 40–64). Nine of these 28 breast cancers (or 30.11 per cent) have a malignancy index above the general average index of 56.04, and 8 of the 31 cervical cancers (or 25.81 per cent) are above the general average of cervical carcinomata of 55.76. The average malignancy index of 26 breast carcinomata with End-result 2–4 is 59.88, while that of 40 cases of cervical cancers with End-result 2–4 is 59.39. Nineteen of these 26 cases of breast cancer (or 73.07 per cent) have a malignancy index above the general average malignancy index, while 40 cases (or 58 per cent) of the 69 cervical carcinomata have a malignancy index above their general average malignancy index.

Table III shows that the malignancy index has a tendency to be higher in cases which take a rapid course than in those with a slow course.

TABLE V

SPECIAL CELL TYPE AND MALIGNANCY INDEX

Cell Type	Cervix	Breast
Cell type 1	45.67 (range 38–54)	40.5 (range 40–41)
Number of cases	9	2
Cell type 2	48.62 (range 32–68)	51.75 (range 44–62)
Number of cases	61	16
Cell type 3	54.65 (range 37–70)	54.70 (range 47–70)
Number of cases	106	43
Cell type 4	60.76 (range 41–75)	56.41 (range 42–72)
Number of cases	49	91

Table V (above) permits the conclusions that the special cell type or the degree of differentiation runs to a certain extent parallel with the degree of histological malignancy in the respective types. But it is also apparent that the evaluation of a carcinoma by the method of the malignancy index gives far more reliable results than the grading of carcinomata on the basis of cell type or degree of differentiation. The differences between the average malignancy indices of the different cell types are not marked enough to indicate definite differences in malignancy and prognosis for most of the groups.

TABLE IV

DISTRIBUTION OF CARCINOMATA IN THE MALIGNANCY GROUP

	Cervix	Breast
Group 1 (32–44)	16.82 per cent (38 cases)	2.94 per cent (4 cases)
Group 2 (45–56)	42.92 per cent (97 cases)	36.76 per cent (50 cases)
Group 3 (57–68)	36.72 per cent (82 cases)	56.62 per cent (77 cases)
Group 4 (69–80)	3.54 per cent (8 cases)	3.68 per cent (5 cases)

GENERAL TYPE OF CARCINOMA AND MALIGNANCY INDEX

The relation existing between the general type, the malignancy index, and the prognosis of a carcinoma was studied to ascertain if highly cellular tumors are more malignant than oligocellular (zellarm). For this purpose the average malignancy indices of the carcinomata of the General type 4 were compared with those of the General type 1. cers of the breast the stroma contributed on the average 12.00 points to the malignancy index; in medullary cancers of the cervix the stroma added 11.28 points, while in scirrhous carcinomata of these organs only 9.67 points (breast) and 9.9 points (cervix), respectively, were contributed to the malignancy index by the stroma. The differences are 2.33 points for the breast and 1.38 points for the cervix. If these observations are taken into account, it becomes evident that

TABLE VI

AVERAGE MALIGNANCY INDEX

	Cervix	Breast
General Type 4	54.11	57.44
Number of cases	120 (53.33% of total number)	65 (47.06% of total number)
General Type 1	52.30	55.16
Number of cases	20 (8.89% of total number)	19 (13.97% of total number)

One may state that, in general, cellular or medullary growths are more likely to have a loose, vascular stroma, with a more or less marked round-cell infiltration, while the rather oligocellular or fibrous or scirrhous cancers show usually a fibrous or hyalinized stroma, with few vessels and scant round-cell infiltration. Deviations from this rule occur, but have not been taken into consideration.

The numerical difference between cancers of General type 4 and General type 1 is three points, if all other factors are equal. As is apparent from Table VI, the actual difference is less than anticipated (1.81 and 2.28). Moreover, one has to consider that the antiblastic status of medullary cancers is usually less marked than that of scirrhous ones. This statement is substantiated by the following figures: In medullary can- the parenchyma of scirrhous cancers is more malignant on the average than that of medullary tumors. The blastic qualities of the parenchyma of a scirrhous cancer of the breast surpass by 3.05 points (0.72 plus 2.53) and those of the cervix by 2.58 points (1.81 plus 1.39) those of the medullary tumors of the respective organs.

CONCLUSIONS

1. A description of the determination of the histological malignancy index and the classification of the clinical groups based on the extent of the carcinoma has been given.

2. The histological malignancy indices were determined in 225 cases of carcinomata of the uterine cervix and 136 cases of carcinomata of the breast. The end-results were known in 100 cases of cervical and 71 cases of mammary cancers.

TABLE VII

CARCINOMATA OF THE UTERINE CERVIX WITH KNOWN END-RESULTS

Journal number	1	3	4	5	6	7	8	9	10	11	14	15	16	17	21	22	24	25	29	30
Malignancy index	69	70	54	57	55	62	54	63	65	64	67	47	61	51	52	53	56	67	53	58
Clinical group	3	R3	R3	3	3	4	3	4	3	2	R3	2	Ad R1	Ad R3	R4	2	3	2	3	Ad 3
End-result	4	4	3	3	1*	2	3	4	2	4	3	1	1*	4	4	2	3	4	1	2
Journal number	31	33	35	37	40	41	45	46	47	48	49	51	52	53	55	57	58	61	62	63
Malignancy index	66	52	54	37	64	49	62	47	49	64	40	75	64	62	61	52	55	50	55	38
Clinical group	R3	R4	4	4	Ad R4	3	3	3	Ad 3	3	3	Ad 3	3	4	4	3	4	3	2	R3
End-result	3	1	3	4	4	1*	3	1*	1*	3	1*	3	2	4	4	1	4	1*	1	2
Journal number	65	66	68	70	71	72	73	74	76	77	78	79	83	85	86	87	89	90	92	93
Malignancy index	72	47	45	56	47	56	53	64	62	63	57	74	41	61	57	41	66	44	54	44
Clinical group	3	Ad 3	4	3	Ad 2	2	3	3	4	3	3	4	3	4	4	Ad 4	4	3	4	2
End-result	3	1	3	4	3	1	3	1*	3	3	1	4	1	4	1	4	4	1	3	1
Journal number	95	96	98	99	100	107	111	118	121	122	131	149	175	176	177	178	179	180	181	182
Malignancy index	54	45	49	52	45	46	68	60	49	55	63	59	55	62	45	64	65	39	67	54
Clinical group	4	Ad 1	R4	Ad 4	R3	1	3	4	3	4	1	2	Ad 1	Ad R3	4	3	3	4	4	3
End-result	1	1	3	3	3	1	2	4	2	4	1	4	1	3	4	3	3	2	2	1
Journal number	184	185	186	187	189	190	192	194	195	198	199	201	202	205	206	208	210	217	218	222
Malignancy index	62	61	57	62	66	60	49	55	48	53	52	60	64	61	47	45	49	59	50	48
Clinical group	2	Ad 2	Ad 3	Ad 4	Ad 4	4	Ad 4	Ad 2	Ad R3	4	2	4	3	3	4	4	4	3	R3	4
End-result	1	1	2	4	4	3	2	4	2	4	1	4	1	4	4	2	4	4	1	4

TABLE VIII

CARCINOMATA OF THE BREAST WITH KNOWN END-RESULTS

Journal number	1	2	3	6	7	8	9	10	12	13	15	17	18	20	21	22	24	26	27	28	29	30	31	32	33
Malignancy index	67	64	60	69	59	52	66	57	58	47	49	66	62	52	51	50	51	61	64	55	59	61	64	72	59
Clinical group	R4	R4	P4	P4	P3	P3	P3	R4	P4	P2	P2	R4	R3	P2	P4	P1	R2	R4	P4	P3	P3	P2	R4	P4	R4
End-result	3**	4**	2**	3**	1**	1**	4**	3**	3**	1**	2**	3**	2**	1**	3**	1**	1**	3**	4**	1**	1**	1**	4**	4**	3**
Journal number	34	36	37	38	39	42	43		46	47	49	50	52	53	56	60	65	69	74	77	78	80	82	84	85
Malignancy index	56	57	60	51	52	65	70		69	58	52	58	46	62	49	66	40	63	45	57	57	49	54	64	60
Clinical group	R4	P2	P3	P3	P3	P2	P3		P3	R	P3	P4	R4	R2	P2	P3	P1	P	P3	P4	P3	P4	P2	P2	P4
End-result	4**	1**	1**	1**	1**	3	3		4	3**	2	4	3	3	1	2	1	1	1	3	2	2**	1	1	3
Journal number		87	88	93	95	97	101	104	105	106	107	108	109	110	111	114	116	117	119	122	123	125	126	128	131
Malignancy index		50	58	50	51	51	48	44	59	49	57	45	50	47	55	57	63	63	58	61	67	51	61	59	69
Clinical group		P2	P2	P3	P2	P2	P3	P3	P3	P3	P3	P3	P2	P1	P3	P3	R1	P3	P3	P3	P1	P1	P3	R1	R3
End-result		4	1**	1	1	1	1	1	2	3	3	3	1	1	3	1	3	3	1	4	2	1	1	1	4

NOTE: Cervical carcinomata with an asterisk represent five-year cures. Breast carcinomata with a double asterisk indicate post-operative roentgen treatment.

3. The prognostic value of the histological malignancy index was tested against the end-results obtained. The result is that the malignancy increases with an increase in the value of the malignancy index. In Malignancy Group 1 the good end-results were 100 per cent in breast carcinomata and 80 per cent in cervix carcinomata. In Malignancy Group 2 the good end-results were 60 per cent in breast cancers and 50.7 per cent in cervix cancers. In Malignancy Group 3 the good end-results were 37.5 and 25.8 per cent, respectively, while in Malignancy Group 4 good end-results were not obtained in a single instance.

4. The clinical grouping gave relatively similar values. The five-year good end-results in Clinical Group 1 were 69.23 per cent in breast cancers and 78.27 per cent in cervical cancers. In Clinical Group 2 they were 51.72 and 31.68 per cent, respectively; in Clinical Group 3 they were 11.77 and 12.42 per cent, respectively, and in Clinical Group 4 they were 3.23 per cent and 0, respectively.

5. The study of the degree of histological malignancy and the extent of the growth gives valuable data in the prognosis and treatment of carcinomata of the breast and uterine cervix.

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RADIUM AND X-RAY THERAPY AS PALLIATIVE MEASURES IN THE TREATMENT OF RECTAL CANCER[1]

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EXCLUSIVE of the stomach and oral cavity, approximately 60 per cent of the remaining intestinal cancers are indigenous to the rectum. Rectal cancers are notoriously difficult to cure because 40 to 50 per cent are inoperable when first seen by the surgeon; the rectum is in daily use; the tumor mass is not easily accessible; the degree of dissemination cannot be estimated by physical examination; the complete removal of all cancer-bearing tissue is a difficult operative feat accompanied by a high immediate mortality.

THE PATHOLOGY OF RECTAL CARCINOMAS

Epithelioma or squamous-cell carcinoma of the anus is uncommon, aggregating only 3 to 4 per cent of all rectal cancers. Its site of predilection is at the mucocutaneous junction in the mid-line, anteriorly. It forms a nodular, warty, flattened growth which tends to ulcerate and involve the rectum proper. Its radiosensitivity corresponds with that of the lip and the buccal mucosa; the most satisfactory plan of treatment is irradiation by the interstitial deposition of small metal-filtered radon implants, known as gold or platinum seeds.

The remaining cancers of this region are adenocarcinomas, which are also the most frequent tumors. The symptomatology, growth tendencies, and pathology of these differ according to their location in the rectal canal. At the rectosigmoidal junction the tumor early encircles the bowel to form an annular stricture. The majority of carcinomas of the rectal ampulla begin on the posterior wall. The four common types of adenocarcinomas of this region are:

(1) The papillary carcinoma.

(2) The malignant adenoma, or adenoma destruens.

(3) The colloid, or gelatinous carcinoma.

(4) The scirrhus or fibrocarcinoma.

The papilliferous, or papillomatous, carcinoma resembles the benign papilloma somewhat, except for the invasive nature of its base. This tumor may be frankly malignant from its onset, or it may be a malignant degeneracy of the benign papilloma. Its growth energy is expended largely by evertent or surface proliferation, producing a bulky exuberant tumor, before the bowel wall is infiltrated. This cancer is readily amenable to surgical extirpation; when radium therapy is to be employed, the papilliferous fronds are removed by surgical endothermy and gold or platinum filtered radon seeds are implanted into the base of the cancer.

The scirrhus or fibrocarcinoma is a peculiar type of rectal carcinoma, exhibiting desmoplastic tendencies, in which the atypical cancer cells are growing diffusely and are nestled away among wide strands of new connective tissue. This cancer is markedly radioresistant.

The colloid or gelatinous carcinoma is a degenerative type of adenocarcinoma. It usually forms a bulky, massive growth in which gelatinous or mucoid material replaces the tumor tissue. It likewise does not respond well to radiation therapy.

Adenoma destruens is the most common type of cancer of the rectum. It may appear early as a cancerous plaque, later forming a malignant ulcer due to the necrosis

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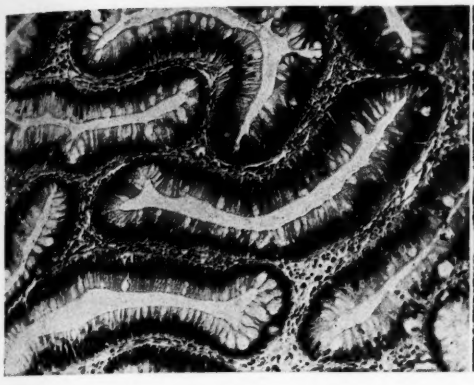

Fig. 1. Rectal cancer (adenomalignum), Grade I, radioresistant, very low degree of malignancy.

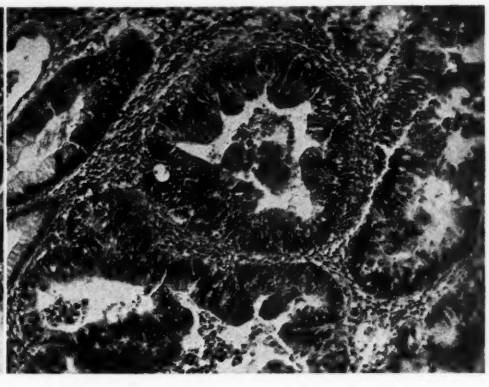

Fig. 2. Adenoma destruens, Grade II, radioresistant.

of the overlying surface. The tubules and their component cells may be quite similar to normal tissue in some instances, insomuch as there is much variation in the histological character and malignancy of these tumors. Only too frequently they penetrate the muscularis mucosa, early and deeply, with the formation of solid, medullary or cord-like masses of cells or irregularly arranged acini within the submucosa. Secondary infection and trauma cause ulceration, which hastens the dissemination of the tumor. The malignant ulcer is crater-like, with indurated elevated edges, occurring for the most part in the lower part of the rectum and at times encroaching on the sphincter.

With consideration of the fundamental principle of cell-differentiation, Rankin and Broders (9) have formulated a histologic classification of the grades of malignancy found in rectal carcinomas. Their conclusions have been substantiated by the studies of Stewart and Spies (12) on biopsy specimens of rectal cancers. These authors and others use four degrees of differentiation: Group or Grade I, Highly differentiated, adult-cell, radioresistant adenocarcinomas; Grade II, less differentiation and slight radioresistance in these adenocarcinomas; Grade III, still less differentiation but slight radiosensitivity in these adenocarcinomas; Grade IV, differentiated, anaplastic, cellular radiosensitive adenocarcinomas.

THE DISSEMINATION OF RECTAL CANCER

A knowledge of the lymphatic drainage of the rectum is essential in order to place properly interstitial foci of radon and thereby anticipate and prevent the dissemination of rectal cancers. Miles (7) has recently classified the lymphatic supply of the rectum in a comprehensive manner; his arrangement is herein given:

1. The intramural lymphatics in the wall of the rectum form two plexuses which communicate freely by channels radially arranged. These two plexuses are arranged in the following manner:

(a) The submucous plexus consists of a network of lymphatics in the ampullary portion of the rectum, which communicates with the lymphatics of the pelvic colon and of the anal canal.

(b) The intermuscular plexus is continuous with the lymphatics of the pelvic colon and those which supply the external sphincter.

2. The intermediary rectal lymphatics

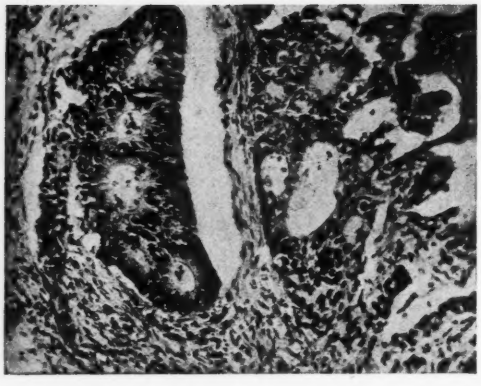

Fig. 3. Adenocarcinoma of rectum, Grade III, radioresistant.

consist of a subserous network beneath the peritoneum of the upper part of the rectum, and a lower communicating lymph space, or cistern, situated between the external muscular coat and the perirectal fat in that part of the rectum not invested with peritoneum.

3. The extramural lymphatics of the rectum spread in three directions: inferiorly, laterally, and superiorly.

(a) Inferior efferent lymphatics. — These lymphatics supply the peri-anal skin, the external sphincter muscle, and the ischiorectal fat. The anal integument has an abundant lymphatic network, from which three to five vessels pass on either side to the inguinal region and end in the medial superficial inguinal nodes.

(b) Lateral efferent lymphatics.—These extend outward between the levator ani muscles and the pelvic fascia. The peritoneum is in close relationship with the lymphatics of the pelvic fascia. Other efferents leave to drain into the internal iliac glands. Anastomoses occur with the lymph vessels of the uterus, vagina, bladder, broad ligament, or prostate.

(c) Superior efferent lymphatics.—This is the most important zone for the spread of rectal cancer. These lymphatics accompany the superior hemorrhoidal veins and enter the lowermost mesocolic (retrorectal) glands. They accompany the inferior mesenteric vein, to empty into a group of glands called the aortic or median lumbar glands.

These are the three ways in which cancer of the anorectal region is disseminated, *viz.*: direct extension or by continuity; lymph spread by permeation of the lymphatics or lymphatic embolism, and metastases by the blood-vascular system. Direct extension is the first process to be initiated; lymphatic spread is next in time and frequency and is of the most surgical importance; embolic metastasis by the blood stream occurs late in the history of the disease, but there are instances where distant metastases have occurred with a quite small primary growth.

Local extension is the result of the infiltrative invasive tendencies of the rectal cancer. This converts a movable cancer nodule in the mucous coat into a fixed growth, inseparably fused with the muscular layer. Although the advancement is in all directions, the most rapid spread is transversely, particularly at the rectosigmoidal junction. The microscopic growing edge burrows freely under the mucous membrane, a fact of which the radiologist must be cognizant, that he may place some radon seeds well beyond the palpable border of the tumor.

The lymph spread of cancer may follow any of the lymphatic pathways previously described. The submucous lymphatic plexus is composed of lymphatic vessels which encircle the bowel, whereas the intermuscular plexus runs longitudinally. It is extremely likely that this is one reason for the tendency of cancer to encircle the bowel wall, because little groups of cancer cells can be discerned at some distance from the primary growth and later form submucous nodules which surround the periphery of the tumor. In cancer of the anus, both the rectal and inguinal glands may be involved as well

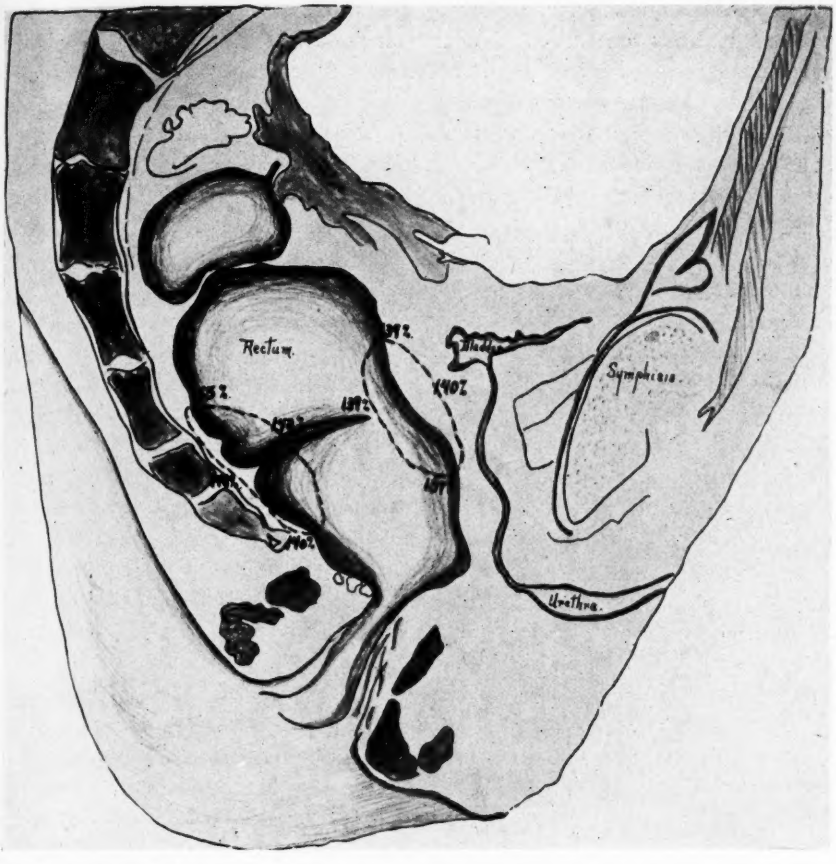

Fig. 4. Tissue dosage estimation in rectal cancer. Small patient: six portals (two anterior, two posterior, and two lateral), high voltage X-radiation.

as the external sphincter muscle, the peri-anal skin, and the ischiorectal space. This lymphatic spread involves the same viscera as in direct extension, but at a much earlier date.

The practical application of this knowledge to the treatment of rectal cancer depends on the proper placement of radioactive foci—gold or platinum radon seeds superficially in the submucosa of the rectum for the same segment of rectum in which the cancer occurs, in order to care for the circular spread by the submucous lymphatic plexus; gold or platinum radon seeds in the wall above and below the cancer, in order to care for the longitudinal spread by the intermuscular lymphatic plexus; the placement of similar seeds or radium element needles in the peri-anal region, the external sphincter muscle, and in the ischiorectal fossa, the treatments to be given supplementary to the direct treatment of the tumor mass.

RADIATION THERAPY OF RECTAL CANCER

What rectal cancers shall be treated by irradiation? Will irradiation alone suffice for the treatment of operable cancers? The radiologist rarely has the opportunity to treat a rectal cancer in its operable stage; usually he must be content with his efforts

to treat inoperable carcinomas and carcinomas recurrent after operation. Under these conditions, the physical agents, namely, X-ray and radium, are decidedly at a disadvantage if statistical analyses for curative results are made, unless one considers the stage and extent of the disease at the time of the initial radiation treatment.

An early biopsy, with histologic grading of the tumor, is of aid in the determination of the radiation procedure. If the cancer is deemed operable and histologically it is graded I, then surgery alone is the procedure of choice because radiation is wasted on such a tumor. Carcinomas graded II, III, and particularly IV, which are considered operable, should receive at least one pre-operative cycle of X-irradiation about the pelvis. No surgeon, however prejudiced he may be in favor of surgery over radiation therapy, should ever operate on a patient with rectal cancer until a biopsy has been done, with histologic grading of the cancer. The cellular, anaplastic, undifferentiated rectal cancers of Grade IV are not only the most malignant rectal tumors but they are also easily disseminated by the surgeon's knife; fortunately they are radiosensitive tumors, so we are justified in considering heavy external irradiation as an imperative and life-saving preliminary measure in the treatment of these particular cancers. Even if cure by external irradiation cannot be effected, the palpable diminution in the size of the tumor, the increased ease of operation, the amount of growth restraint, and the inactive state of this type of cancer as affected by external irradiation, favor the success of the later operative removal. The radical excision of the rectum should be delayed for at least four weeks after the pre-operative external irradiation.

What can the surgeon do for patients with inoperable rectal cancer? The answer is, "Nothing but colostomy." In inoperable cases are radium and X-ray treatments palliative measures? Do they relieve suffering? Do they prolong life? The answer is in the affirmative. What determines the inoperability of a rectal cancer? I would answer: "The immovability of the tumor mass, direct infiltration of the prostate, uterus, or bladder, distant metastases or an impaired general condition of the patient such as advanced age, advanced tuberculosis, heart disease, etc." Occasionally, cases are considered inoperable at first examination which are later deemed operable after the effects of the irradiation are made manifest; such instances are not common, but they certainly do occur. When palliation only is indicated, the radiologist should make no attempt to cure an advanced rectal cancer with radium or X-rays, or both, because this entails a drastic procedure. In such an instance the patient's tolerance and health should be conserved by a prolongation of the period of irradiation over several weeks, using interrupted and weak treatments repeatedly to secure growth restraint and induce abortive fibrosis in the cancer. When a curative effect is planned, all the radiation treatment should be given within eight or ten days. Liver metastases are treated cautiously with suberythema doses from three directions; they respond fairly well to tissue dosages of 110 per cent of an erythema unit, but the three treatments should not be given within a short period of time.

Before the rectal cancer is irradiated, a colostomy, or the forming of an artificial anus, should be done. The reasons for this are as follows: *(a)* the diseased part should be put at rest; *(b)* the shunting of the fecal current will permit the infection of the ulcerated cancer to be treated; *(c)* it permits exploration of the abdomen and the determination of the extent of the cancer and its regional and visceral metastases, if present; *(d)* at a later date the fibrosis following the radium therapy may partially

occlude the rectal lumen. Some men, such as the French surgeon Proust, of the Hospital Tenôn, will not treat rectal cancer unless the patient consents to a preliminary colostomy. Radiologists must appreciate the necessity of laparotomy, as this affords one of the best avenues for the insertion of radon seeds into the primary tumor as well as into any outlying metastases to lymph nodes. It is fallacious to expect control of the cancer by the energetic irradiation of the primary lesion when the anorectal, retrorectal, and paracolic lymph glands are involved. Sir Charles Gordon-Watson inserts the radium-bearing implants into the rectal cancer by the transperitoneal route at the time of this laparotomy.

Within a few days after the colostomy has been performed, the irrigation of the lower loop is begun, using 5 per cent sodium bicarbonate solution for cleansing purposes. In the absence of feces and with continual irrigation the infection subsides and the tumor seems to become smaller. Two weeks after the colostomy is made, a pelvic cycle of X-irradiation is given, followed almost immediately by interstitial radium therapy. The colostomy opening, or stoma, is pro-

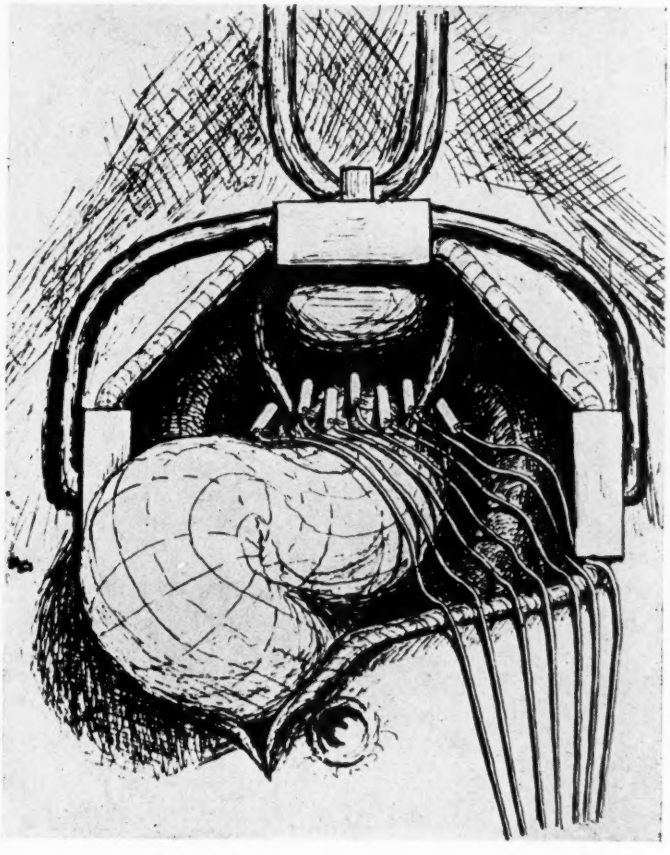

Fig. 5. Transperitoneal insertion of radium-bearing needles into rectal cancer. Technic of Sir Charles Gordon-Watson.

tected by leaded rubber in order to prevent injury by the X-rays to the delicate susceptible mucosa of the colon.

In a pelvic cycle of external irradiation, usually by X-rays, we employ four or five fields; two anterolateral fields and two posterolateral fields, including the sacral area. Care must be taken to prevent overlapping of the skin portals. When the cancer is situated low in the rectum, a perineal portal may be added, in which case only 80 per cent of an erythema dose is given to the area because of the sensitiveness of the vaginal and anal mucosa.

The tolerance of the small and large intestines to X-rays should be considered. Wintz states that the small will tolerate 30 per cent more irradiation than will the large intestine. May gives the following degrees of reaction of the intestines to various tissue doses of radiation: 80 per cent erythema dose may cause a slight erythema of the intestinal mucosa, with an abundant discharge of mucus; 110–120 per cent erythema dose may produce genuine inflammation, with fibrinous exudation and a bloody mucous discharge; 130 per cent erythema dose causes ulceration of the intestinal mucosa. Consequently care must be taken to direct the rays toward the rectal lesion and to secure a homogeneous field of radiation.

External irradiation lessens the hemorrhage from the cancer, diminishes the toxemia from absorption, and later decreases the infection of the rectal cancer. Cancer of the rectum cannot be cured by external irradiation alone. This is because 125 to 140 per cent of an erythema dose, which is delivered to the tumor by a pelvic cycle of X-irradiation, is insufficient to sterilize the most radiosensitive tumor. So-called cures of rectal cancer reported to have been accomplished by external irradiation will be found to be cases which have not been free of disease for five years.

For the employment of local radium therapy, the amount of radium and the filtration necessary depend on the site and size of the tumor and the time of irradiation. Radium applicators for surface application cannot be satisfactorily used in the rectal canal because *(a)* the dose is too superficial; *(b)* the length of time will not permit effective irradiation, and *(c)* there is some danger of the applicator slipping and losing its contact with the cancer. If topical or surface application of radium plaques is to be used as an adjuvant measure in the treatment of flat, ulcerating growths, the patient should be placed in the knee-chest position and the rectum thoroughly packed after the placement of this type of applicator. Then the patient rests in bed quietly without movement during the treatment.

Interstitial irradiation is the really effective method of radium therapy. Metal radon implants of gold and platinum eliminate 97 to 98 per cent of the more destructive energy, so that even slight necrosis does not occur after the implantation of these seeds—success absolutely depends on proper dosage and accurate placement of them. The radium therapist can detect the difference in resistance of cancerous and normal tissue, when the hollow needles are inserted for the deposition of the radon seeds.

After the radon seeds or element needles are inserted in the rectal cancer, the rectum should be packed with rubber tissue to keep the needles well embedded in the growth, to maintain their proper emplacement, to protect the intact mucosa below the growth from the close proximity of the needles or radon seeds, and to allow the free discharge of blood and infected fluids from the surface of the growth.

Frequently we prefer to use radium element needles of 10 milligrams strength and 0.5 millimeter filter. Sometimes ten or fifteen of these needles inserted into the rectal cancer are necessary for effective irradiation; for this purpose we prefer to have the

patient in the lithotomy position under anesthesia. Either sacral or spinal anesthesia is a satisfactory method, or nitrous oxide anesthesia for the short time necessary to introduce the needles or seeds.

All of the rectal cancers are treated from below, but, in addition, certain of them can be treated from above, *e.g.,* cancers at the rectosigmoidal junction are best treated from above and below. An operating cystoscope may be inserted into the colostomy opening from above, and gold or platinum radon seeds introduced into the superior portion of the rectal cancer by special hollow needles; or a small proctoscope or sigmoidoscope may be inserted from above downward and needles with thread attached introduced through the channel.

If the cancer is on the anterior rectal wall of a female patient, the radon seeds or element needles can be inserted into the cancer through the posterior vaginal wall. Excision of the coccyx and exposure of the rectum posteriorly will sometimes afford a better field for the insertion of gold or platinum radon seeds directly into the tumor growth and into the perirectal structures. If element needles are used through the wound, they should not perforate the wall of the rectum nor perforate the cancer if they are inserted into the cancer from the outside. The anus is sewed up previously to prevent contamination. Or the radium element needles may be introduced deeply into the perirectal cellular tissues by puncture of the perineum and anococcygeal raphé with a trocar. This procedure requires rigid asepsis and constant dressing, if it is not to be followed by perirectal suppuration.

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SOME ECONOMIC ASPECTS OF THE CANCER PROBLEM[1]

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THE economics of cancer may be viewed from many angles, two of which will be briefly considered: First, the cost of medical care to the average cancer patient and, second, the influence of cancer upon the civic and domestic life of the afflicted.

It is now generally agreed that cancer in its early stage while still localized may be successfully eradicated, the reliable agents for this purpose being surgery, X-rays, and radium, either singly or in such combination as the individual case may require.

In certain communities it is possible for a patient with little or no funds to obtain curative treatment for localized cancer, and so be restored to a useful position in the world. In other less fortunate communities, however, facilities for the removal of early cancer, especially by other methods than the knife, are sadly lacking. This is one feature of the economics of the cancer problem which cannot be too forcibly called to your attention. In many communities the precious element, radium, exists only in small amounts—too small to be employed successfully. Because of insufficient interest or lack of funds with which to obtain adequate equipment, this form of therapy is frequently unavailable.

And what of the patients' own economic situation? We are confronted here with the stubborn fact that treatment is both long and expensive and that the average patient is unable to pay his doctor even a reasonable fee. For his necessary sustenance he must use the little fund which he may have been fortunate enough to accumulate after many years of toil. He is unquestionably entitled to do this, although it precludes the possibility of meeting the expense of medical care.

The cost of individual treatment by radiation, when applied by the individual physician employing his own agents, must of necessity be high enough to pay the doctor a reasonable fee in order that he may live and progress in his work by improving in his technic.

Yet, when we analyze the relative cost of surgical care, with its accompanying hospital charges, and treatment by radiation in such cases as may reasonably be expected to respond favorably to either method, it will be found that the economic balance is decidedly in favor of the patient treated by radiation. This applies not only to the actual outlay of money, but also to the fact that the period of the patient's incapacitation is markedly less when radiation treatment is undertaken. This is not a plea to substitute radiation for surgery when the latter is clearly indicated, but merely to give the patient an opportunity to have chosen for him or her that particular treatment which will restore the individual to useful citizenship in the most economical and expeditious manner.

The foregoing, however, applies only to the patients in comfortable financial situation, a social group which does not include 80 per cent of the cancer population.

The second part of our discussion, dealing with the industrial and family life of the cancer patient, is so complicated that only in brief outline can the subject be considered in a paper such as this. Consideration of cancer in the young may be omitted, as the economic aspect is negligible. Again, when major cancer attacks those past middle age, we can use only the palliative means at our command. For such cases, institutional care is needed, for the average

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home is not a fit place in which to keep such a patient. As is so often the case, the family has neither the means nor the patience to handle these poor sufferers, and they should rightfully be cared for by the community. Most of these patients have passed the useful period of their life and as the percentage of cures is here a negligible factor, their loss to the community is not a serious one. It is when cancer attacks the wage-earner or the mother of the family that the problem becomes grave, and at once a challenge to the physician, who, in the eyes of the public, is judged competent to cope with all human problems of disease.

Many a man could be spared to his family and to his community if the early lesion of the lip, tongue, or skin received the scrutiny and the care of an effective cancer clinic. Many a mother would be restored to her home if the early intermenstrual bleeding or the primary lump in the breast were properly interpreted.

The economic problem here, however, both to the patient and to the community, is acute. Such a patient demands adequate help, both medical and material. Uncured, the patient becomes a burden upon the community, and the family a public charge. In the case of the mother engaged in rearing her children, the loss in even more serious.

How can we meet the gigantic and manifold problem we, as medical men, are thus called upon to face? Not by an apathetic indifference, nor through failure to recognize the situation, but only by the wholehearted co-operation of the entire medical profession.

Radiation has demonstrated its ability to cope with certain cases of cancer better than any other agent thus far available; but radium must be had in proper form and amount and its use must be directed with trained intelligence before humanity can receive from it the maximum benefit.

It is significant that every medical institution where radium has been available long enough for the demonstration of its value in cancer, is increasing this supply as rapidly as possible. The reason for this is that those working in such institutions have had convincing proof of the efficacy of radium in larger amounts than were formerly used. This fact should become familiar to all medical men.

When the profession is confronted with that ever increasing group of patients in whom cancer is no longer a localized lesion, the best medical skill and equipment should be available (including the ability to use large amounts of radium or short wave X-rays). Otherwise the deplorable lack of the proper facilities for treatment will be acutely realized.

It is estimated that 10 per cent of the human race acquires cancer—a terrible toll, and a challenge to all medical men. Assuming that surgery may be credited with successfully combating 15 per cent of all cancer cases, and radiation treatment an equal percentage (conservatively deduced from five-year statistics), the combination of these two major agents brings the total of cancer cures, if we may use that term, up to 30 per cent. This leaves an appalling balance of 70 per cent of all mortals afflicted with cancer who must die because of our inability to help them.

The large radium packs, sometimes called "bombs" or "cannons," seem to promise additional decrease in this unhappy balance. It is not too much to hope that an appreciable drop in mortality can be brought back thus. A personal visit to the clinics where such packs have been in service one year or more has convinced the writer that radium in this form is a demonstrable step in advance of the fractional dose method, which most of us are compelled to use. The men who employ the "big guns" have all had training for many years with radium in lesser amounts, and they are the ones best

fitted to judge. Without exception, they have indicated to the writer their belief in the efficacy of the new method, and expressed the hope that they will be able to be of greater service to cancer patients than formerly.

It is a good omen to note that all of these men are cautious in their statements. They rightly feel that a great deal of exploitation has already been accorded radium, to the detriment of its scientific status. Therefore it is a pleasure as well as a privilege to state that the most enthusiastic comment elicited from a leader in massive radium therapy is that he believes radium mass in dosage of four grams or more has an action on tumor cells not hitherto achieved, and that he hopes hereafter to obtain better results than ever before. The writer has, for a number of years, been an earnest student of this problem and has felt himself unable to render to the cancer sufferer the full benefit which would have accrued had he been possessed of adequate radium equipment.

It is not intended to convey here the impression that unless one has four or five grams of radium he cannot to an effective degree cope with cancer. Many radiologists with a small amount of fifty or one hundred milligrams can perform excellent work in uterine carcinoma or in suitable local lesions, but such work is strictly limited to private practice and has no bearing on organized community work in dealing with cancer.

No individual physician or group of physicians depending upon their practice for maintenance could set aside funds sufficient to purchase a large working quantity of radium—meaning a minimum quantity of four grams. This amount at the present market price costs $228,000. Placing this in the proper cannon or bomb for service, and adding other necessary equipment, would increase the price to some $300,000. It need hardly be emphasized that such a radium container must be placed in a suitable location surrounded by all necessary protective factors, and, most important of all, in the hands of those only who are qualified by training and experience to use it safely.

Up to a very few years ago, radium clinics were almost unknown. In America there were only two units, and two in Europe. To-day in Europe alone, approximately 35 grams of radium is in use—an amount exceeding the world's entire supply ten years ago.

There are probably in the world to-day not more than fifteen medical centers where radium in sufficient quantity to cope successfully with major cancer work is available. These centers are approximately equally divided between the two hemispheres. In America, 80 per cent of the radium depots are in the extreme eastern part of the country. In Europe, practically all the radium is located in the countries bordering the North Sea.

In view of all the foregoing facts, we are confronted with the problem of providing properly equipped clinics, available to patients of varied financial status; of increasing our supply of radium, and of educating the public—and to a degree the medical profession—as to the specific value of radiation treatment, in addition to the other means at our command.

The first two requirements involve financial difficulties. The help of municipalities or states might be obtained in some cases; in others, private aid would be forthcoming. There are in America not a few wealthy and philanthropic individuals who might be interested in helping such a cause if they were made acquainted with the facts, and it is sincerely to be hoped that a movement to enlist their help will be organized without delay.

The distribution of cancer clinics should follow a well directed, country-wide plan.

It would be poor practice and economy to scatter fractional amounts of radium in small communities, or in several centers in large cities.

Whether such clinics could be placed on a basis which would make them self-supporting, after the primary outlay was secured, can not be predicted with accuracy. Many patients could contribute something to the upkeep, and well-to-do patients might be more liberal. However, the clinical center might even then need to be subsidized to some extent.

With such cancer clinics established, it would not take the public long to realize that here was real help available in certain definite fields. By the same persistent and cooperative methods as were inaugurated by Finsen, of Copenhagen, in the campaign to stamp out lupus, we may hope for parallel results with cancer. In the space of approximately twenty-five years, lupus has become a comparatively rare disease instead of a widely prevalent scourge.

To best achieve the desirable ends under discussion will require painstaking and persistent work—a relentless publicity campaign in which all medical men should unite. The public must be given the facts and continuously urged to come to their doctor at the first unusual symptom. When they learn that cancer is curable in case the primary lesion can be destroyed, their confidence will be gained, and little by little the secondary and tertiary stages of cancer will lessen in frequency.

This may seem a long path and the writer's viewpoint may be criticized, yet he believes that when the whole question of cancer is fairly before us and when all actual facts which have been accumulated are critically analyzed, one will acknowledge that there does not seem a reasonable prospect of finding in the immediate future a specific remedy for this dread disease. We must, therefore, increase to the fullest extent the effectiveness of the means which are at the present moment under our command.

DISCUSSION

DR. GEORGE E. PFAHLER (Philadelphia): In the first place, I believe that we should get help in 90 per cent of these cases of carcinoma involving the accessory sinuses, as we see them in Philadelphia, from a study by means of the roentgen rays, insteady of 5 per cent. Certainly that is our experience. It may be that Dr. Quick gets these cases in a much earlier stage, and I believe that probably in the earlier stage the X-rays will not be of great help in making a differentiation. One of the chief factors in the diagnosis of carcinoma in any part of the body is invasion, and if, in the study of the accessory sinuses, you can establish invasion, and if you have carcinoma involving, for example, the maxillary sinus, there is apt to be invasion of the surrounding structures, and you will get erosion and decalcification of the neighboring bones; then it is rather definitely localized. That is, it is not a general decalcification affecting all the bones of the face, but, rather, the bones in the region of the tumor area. It can be traced back into the ethmoid cells, and if those cells are destroyed, and particularly if they are destroyed on one side, one recognizes the condition as one of carcinoma. If there is erosion in the floor of the orbit, in the inner wall, or in the superior wall of the orbit, when the ethmoid cells are involved, there is present an indication that one is almost certainly dealing with malignant disease.

I agree with Dr. Quick in that we must judge each particular case by itself and adapt our treatment to the individual case in hand. If the patient needs drainage, drainage must be established; but I also agree with him that we must not operate merely for the sake of taking away part of the tissues. I believe, with him, that a microscopical study and a biopsy should be

made with as little trauma as possible, excepting only instances when that trauma must be done for the sake of establishing drainage or finding means of applying radiation to the disease.

I agree with Dr. Widmann that the method which he has described and which, as he well knows, we have used in our office for about three or four years, is highly effectual. It is based chiefly upon the second principle brought out by Regaud, namely, that the more highly filtered your radium is, the less damage there will be to the normal tissues, and by this high filtration and the prolonged irradiation which is possible as a result, you are also to destroy the carcinoma tissue with little or no damage to the normal tissue. I made a report on this subject before the international conference on cancer in London last Summer, and it was a great satisfaction to me, when I visited the radiological institute—the Radiumhemmet—in Stockholm, and the Radium Institute in Paris, to find that they were using exactly the same method, namely, high filtration, prolonged irradiation, and radium packs wherever there was room or opportunity to apply them. They were thereby getting results with almost no destruction of normal tissues, and that is the principle. Inside the mouth you cannot use radium packs. You must, by means of these lead applicators, as Dr. Widmann has described, apply them in different parts of the mouth. I commonly use 2 mm. of platinum, which is equal to about 4 mm. of lead, but anywhere from 1 to 2 mm. of platinum—1 mm. of platinum in filtration is equal to about 2 mm. of lead. By this high filtration, one gets a tremendous effect on the cancer cells without great damage to the normal tissue cells, and I think that is the great secret of success. I have had the experience in four cases of getting complete disappearance of the cancer after it had invaded the interior of the maxillary bone—clearly demonstrated, so that there could be no question as to the invasion—and get complete recovery, with retention of the bone structure. While I was visiting the Radium Institute in Montreal in October a year ago, Dr. Gendreau showed me two cases, with involvement of the lower jaw bone, in which he had obtained just those results, namely, recovery by the use of this very highly filtered radiation. More and more I am using 2 mm. of copper filtration in connection with high voltage rays. Now perhaps the physicists say there is no difference, and some of the biologists claim there is no difference in the tests they have made, but from a clinical standpoint there is no question about it in my mind—that the high filtration gives different results from those you obtain from the lower filtration. Even in the book translated by Dr. Schmitz, Friedrich's experimental work, you will find it recorded that the biological effect for the same amount of intensity of irradiation is two and a half times as great when you are using pure gamma rays as when you are using any of the various grades of X-rays. This writer found, as probably all of us have found, that in proportion to the intensity delivered to the affected parts, there is practically no difference between no filtration and up to half a millimeter of copper, but I do believe that we have unquestionably better clinical results.

Dr. Soiland has struck the keynote of the whole cancer problem in urging that we educate the public to the importance of early recognition of cancer and the early and complete treatment from the very first sign of it. If we can do that, many of these other problems will disappear.

Dr. Douglas Quick (closing): Just one word about the paranasal sinuses in order that Dr. Pfahler may not misunderstand what I was saying about radiographic diagnosis. I was referring to those cases in which we would have to depend entirely upon films to make a definite diagnosis of

malignant disease. We get a great deal of help, of course, from films in the more advanced cases, where we can clinically determine pretty much the same thing by various direct examinations alone. If we could get more help in the earlier diagnoses of these lesions and the differentiation of them from the inflammatory processes, we would be a good bit ahead. May I add one word to Dr. Widmann's paper, anticipating his closing later?

THE CHAIRMAN: Certainly.

DR. QUICK: I just want to add a word of appreciation of Dr. Widmann's presentation on combining the various qualities of radiation. I believe we sometimes think too much of the quantity of radiation and give too little thought to the quality. While, from the biological standpoint, some of the clinical observations are not entirely supported, I think the more we have clinical observations from different centers and clinics, the more we will be encouraged in believing in them. We have felt that the shorter wave length of heavily filtered radium, in combination with X-radiation, permits considerable clinical advantage over using the radiation of just one type. I was particularly interested in the diagram of irradiation within the mouth, showing the rather uniform distribution in percentage of erythema throughout the tumor-bearing area. I wish Dr. Widmann would tell us, in closing, something of the histology of these metastatic growths in which metastatic cervical nodes regress on gross examination for a temporary period. I ask that for two reasons, the first of which is because of the percentages which he had on that slide, which were around three, four, and five erythemas. There are certain of the embryonal epidermoids, transitional cell types, etc., which three or four erythemas, or occasionally even less than that, will apparently completely clear up. With the adult type, however, it has been our experience that it takes seven to ten erythemas to actually eradicate the disease, and I cannot get that out of mind, when we see what would appear at times to be rather unusual results. Sometimes I wonder if masses that seem to disappear permanently, metastatic from adult types of growth, may not have been put down on the record as metastatic, but are probably in the end inflammatory. I wonder if we sometimes do not misinterpret bone changes about the jaws when they are inflammatory rather than definite extensions into the bone. We have had difficulty aplenty with the secondary invasion of bone in adult types of epidermoid carcinoma, and except where occasionally a large area of bone is completely devitalized by irradiation and later exfoliated, I have not seen definitely proven secondary invasion of bone cleared up by any type of irradiation without sequestral separation.

DR. PFAHLER: Dr. Quick has asked me to make an explanation which I took it for granted was understood. In speaking of these bone carcinomas, we give as high as sixty thousand milligrams of radiation externally, and we give three to four thousand milligram-hours inside the mouth. All of this treatment to affect a carcinoma of the jaw is not given externally, but is given intra-orally, as was indicated in Dr. Widmann's paper, and I took it for granted that that was understood.

DR. HENRY SCHMITZ (Chicago): The papers presented hardly permit of a discussion. They are of so masterly a character and are based on such a vast number of observations that little can be added. The results given correspond to those published in the literature. Dr. Healy stated that priority for the combined X-rays and radium treatment in carcinoma of the cervix should be credited to Dr. Bailey. If Dr. Bailey started the method in 1915, I preceded him at least by one year. I wish to say that we have used the small field method since 1912.

We added radium to the X-ray treatment in the beginning of 1914, and the first report of this work which we had done was made at the meeting of the American Medical Association at San Francisco in 1915.

As far as the histological grouping according to the predominating cell type is concerned, we feel that the cell type alone is not as reliable an index of the degree of histological malignancy as the study of anaplasia, differentiation and undifferentiation, and the behavior of the stroma. I shall consider these factors in a paper to be presented this afternoon.

There is a tendency in the various clinics to increase the radiation doses, especially in the prickle-cell and transitional cell type cancers. This change in treatment may be attributed to the scientific investigations of the radiosensitivity of tumor cells by Ewing. Ewing's work has influenced radiology more than any other factor. It has taught us to corroborate our clinical observations with pathological evidence. Ewing's deductions are so logical and so scientific that it has been impossible to refute them by any means whatsoever.

EDITH H. QUIMBY, M.A. (New York): I should just like to describe briefly the way in which we derived those tissue doses Dr. Healy presented. The method of determining tissue doses due to X-rays is well known and need not be discussed: the dose close to a small source of radon actually placed within the tissues is quite another matter. For the bomb and the tube we have used the method of submerging both the radiating source and the measuring ionization chamber in the water phantom, and determining the relative intensity of radiation at different distances from the source. For positions close to the source, the possible error is rather large, due to the size of the ionization chamber relative to the distance considered. For larger distances this factor is less important. These measurements gave only relative intensities. For the actual erythema dose, that is, the amount of radiation from a tube necessary to produce a threshold erythema, a different type of experiment was necessary. The tube was embedded to a known depth in beeswax and strapped to the skin of patients for varying lengths of time until the dose was found which produced a faint erythema in 80 per cent of all cases and no visible effect in the other 20 per cent. This is 150 mc.-hr. through a centimeter of wax, or tissue. Then a treatment of 1,000 mc.-hr. with a single tube would deliver 6⅔ erythema doses at a distance of 1 centimeter. The data obtained with the water phantom permit the calculation of the erythema dose for other distances. The erythema dose for the bomb has been determined in a similar but somewhat more complicated manner. On Dr. Healy's figure, the doses indicated for the points very close to the tandem are very great. They are subject to a large error, as I have stated. For these points this is unimportant. We know that they get very much more radiation than they need, but they must, if more distant points are to be adequately irradiated. The doses indicated for points at greater distances represent quite well the amount of radiation actually delivered there. What we hope to do after study of a large number of cases, is to find the amount of radiation which we may expect to produce satisfactory regression, and then to try so to plan our treatments that every part of the lesion shall receive at least this dose.

DR. FRANCIS CARTER WOOD (New York): What impresses me as the most interesting part of the presentation is the convergence of opinion which is so evident—the codification, so to speak, of various technics—the appreciation of the value of histological studies of the tissues, not only of the epi-

thelial cells but of the connective tissues also, and the accurate measurements of dosage, combined with an approach to a standard method of treatment. It is interesting to note also that the early experiments which were done in the laboratory on animal tumors are now being confirmed by the studies on human tumors. In the early publications it was stated that four to six erythemas were necessary to kill all the cells of an animal tumor. We are now appreciating that this amount or even more must be given to obtain cures in human carcinoma. I feel that those who have the large choice of material at their disposal owe to the rest of us who perhaps have not so much, the publication of monographs not only including the clinical history of the case with the results of physical examination, but also photomicrographs of all tumors and vastly more detail as to treatment than we can get from papers of the type read here. The Mayo Clinic, and the Memorial Hospital, of New York, I think, might well issue a complete and detailed atlas of the type of tumors which they treat, together with the results, in order that pathologists throughout the country may learn of the detail of the tumor groupings and the clinical results which have been obtained. There is a good deal of divergence of opinion still as to the grouping types and some criticism of the value, which I think is quite unwarranted. No one thinks that by examining a bit of a scraping from a cervix that a prognosis as to the ultimate cure can be given, because that is only one portion of the condition. After all, the smallest cervical tumor, which any one would think was curable with perfect ease by radiation or by surgery, may already have metastasized to the pelvic nodes, something which can never be determined and the reason, I think, why we still do not get 75 or 100 per cent of cures even in favorable cases. But just such mass material as these large clinics have in their records is invaluable, if it can be given in great detail. There are monographs published on vastly less important matters than these.

It is interesting to hear Dr. Healy say that they treat certain advanced cases with X-ray first. That, as you know, is Regaud's practice. I have seen a patient who could not come into the hospital for a couple of weeks for personal reasons, whom we treated with X-ray. When the time came for the insertion of radium, the tumor had entirely disappeared. The radium was inserted, however, since which time—a year and a half—the patient has been without the slightest symptoms. This shows what can be done by radiation externally as a preliminary cleanup preparatory to the insertion of the radium, which is, however, also necessary, in my opinion, to get the high local dosage required to destroy the tumor cells. After all, we must realize that no matter how carefully we group or how thoroughly we study these tumors morphologically, only an approximate idea is obtained of their biological peculiarities. An experiment which was done in my laboratory by Dr. Woglom and has long since been forgotten illustrates this point. Three breast tumors occurring in the same mouse were transplanted into a large series of animals. These breast tumors are indistinguishable in their morphology, but one tumor took in about 80 per cent of the first inoculations, showing it to be of very high malignancy; another tumor took in about 50 per cent, showing moderate malignancy, and a third tumor took in 8 per cent, which is about the malignancy of a basal-cell tumor of the human skin. These fluctuations can be eliminated only by mass statistics, and a combined study of three or four thousand cervical tumors, with suitable pictures of selected fields, would be an invaluable contribution to cancer. This can be done by two or three large institutions in this country.

It is perfectly evident that the time has passed for surgery of carcinoma of the cervix. It is also perfectly evident that the

general surgeon or the general radiologist is not in a position to treat these patients as effectively as they can be treated in large institutions. The inevitable result must be the concentration in institutions of large amounts of radium, which the ordinary hospital cannot afford to purchase, and the concentration also of patients in special institutions where such treatments can be carried out according to standard methods. I do not agree with many that the treatment of carcinoma of the cervix with radium intelligently and properly is a very easy matter. It requires experience; it requires ample equipment and careful measurements. How many hospitals have a physics department that can carry out the measurements which have been discussed here to-day? How many have a gram or two of radium available for the few cancer patients they will admit? It means, I believe, that ultimately there will be throughout the country special cancer institutes in which the patient suitable for radiation therapy can be treated in the best possible way.

Dr. Harold Swanberg (Quincy, Ill.): There were several points concerning Dr. Healy's paper which I should like to emphasize. The first is in regard to the cervical infection that invariably accompanies cervical carcinoma. I think most radiologists have not appreciated the importance of controlling this condition before proceeding with the radium treatment. There is a tendency among a good many radiologists, as soon as they have diagnosed a carcinoma of the cervix, to immediately apply radium. This, to my notion, is somewhat of a mistake.

We may secure an undue temperature reaction and a severe complication if we apply radium before the patient has had an opportunity to partially recover from the infection that invariably accompanies these cases. Our method of procedure is the same as Dr. Healy is doing, that is, copious, warm, vaginal douches two or three times a day, administered for a week preceding the insertion of the radium. During this same interval, we institute our X-ray treatment. If I understood Dr. Healy correctly, I believe he said that in the majority of his cases he used the X-ray following the radium treatment. Dr. Wood, I believe, interpreted this point differently. We are giving a more intensive, or I might say a more saturated, method of treatment than Dr. Healy is giving. Instead of giving five exposures, our treatment lasts over two or three weeks, keeping the X-ray dose at the so-called saturation point.

If we are going to really accomplish a great deal in the treatment of carcinoma of the cervix, we must adopt a method of treatment that can be generally carried out, because it is impossible to get all of our patients to the few cancer clinics that have a comparatively large amount of radium available. I think the average radiologist should not be discouraged because he does not possess a gram of radium, and that a great deal can be done for these patients with smaller amounts, in the same manner that Regaud is applying it at the Radium Institute of the University of Paris. You will recall that he is using between sixty and seventy milligrams of radium to treat his cervical cancer patients, and I think his results compare very favorably with some of the best work done in this country. Dr. Healy evidently does not think well of long continued radiation as compared to radiation administered in comparatively short periods of time, but, on the other hand, the results he is able to attain are not a great deal superior to those Regaud has secured with the "small amount, long duration" technic.

Dr. George E. Pfahler (Philadelphia): Any report that Dr. Schmitz makes is bound to be instructive, because he goes into the conditions so thoroughly. He has made a real contribution to radiology in his group-

ings, particularly of carcinomas of the cervix. He first gave this grouping at the New Orleans meeting of the American Radium Society, and I am sure that this has helped, to a great extent, to clarify the classification of cases and to help us to determine about what our results should be and what the line of treatment should be. He has carried this on to the study of breast cases, and there can be no question as to the value of this grouping. I agree thoroughly with him that we should eliminate the words "operable" and "inoperable," because the question of operability is influenced by too many factors which vary with the individual operator. In some instances the surgeon is influenced by his interest in the patient, sometimes by his interest in his statistics, and in others merely by sentimental interest; but grouping these cases pathologically or by the extent of the disease will help us in the future to learn what should be done in any particular group under consideration. Now I personally am more impressed by the clinical grouping than I am by the histological grouping, because the important thing, when a patient comes before you, is to know what shall be done with this patient. If you operate in order to get the specimen under the microscope, you have already decided what you are going to do, and while it is of scientific interest to work out these problems and determine how nearly they fit in with the clinical problems, the clinical grouping is certainly of the greatest practical importance. Dr. Schmitz' classifications, both the clinical and the histological, have apparently fitted in very well. I would like to hear, however, in his closing remarks, as to whether the clinical group which he marks "Group 4" corresponds to the histological grouping 4, or whether some of the clinical groups in which the disease was strictly localized also belong to Group 4 of the histological grouping. That, of course, would then necessitate a separate grouping as to the end-results. Dr. Stanley P. Reimann and Dr. Eugene Case, during the past year, have taken a group of breast cases in which the end-result was known, submitted the microscopical specimens to several pathologists, allowing them to classify these cases according to the microscopical findings in these slides. When these end-results were compared with the end-results obtained clinically, unfortunately they did not correspond in any sense. Now, in making a specimen for microscopic study, we must bear in mind that a great deal depends upon the judgment of the pathologist in picking out the particular specimen he puts under the microscope, for it is utterly impossible for the pathologist to examine all of the tissues, and this fact must influence the final grouping. Dr. Schmitz has brought out another very interesting clinical fact, namely, that his figures are 17.5 per cent of cures—five-year cures—counting all of the cases, or, in other words, the absolute cures. These correspond pretty generally with the results that are being obtained throughout the world, and they are very similar to the results obtained whether the patient is operated upon or treated by irradiation. Likewise, the results obtained in the localized and borderline groups, Class 1 and Class 2, according to Dr. Schmitz' grouping, run somewhere between 40 and 45 per cent very generally throughout the world. There, again, the end-results are very similar, no matter whether the cases are operated on or treated by irradiation. We have, however, favored irradiation as the best treatment, eliminating about 17 per cent mortality from the Wertheim operation in carcinoma of the cervix. It would seem that if we can educate the public and the men in general practice to pay attention to the earliest signs of malignant disease and have the cases treated either by radiation or operation, we would get results up in the region of 60 or 70 per cent. I believe if we can spread the information that there is hope of successful treatment of the primary lesion in the early stage

by irradiation, the public—the women who have these carcinomas of the cervix or breast—will be more willing to come for treatment in the early stages.

DR. W. H. MCGUFFIN (Calgary, Alberta): Dr. Soiland has made three statements to which we should give some thought.

(1) "Approximately 70 per cent of our cancer cases are incurable," therefore, from the economic viewpoint we should do all possible to prevent this disease, particularly through the aid of periodic health examinations and public education.

(2) That "80 per cent of the cancer patients are financially unable to compensate the medical practitioner for the necessary treatments." This would seem to justify the Doctor's contention that state assistance is, in part, a solution of the problem.

(3) "The advisability of centrally located cancer clinics for the diagnosis and treatment." Truly we are in accord with this point. It is only necessary to study the splendid accomplishments of such clinics in order to make us realize that this constitutes the ideal method of handling our cancer cases.

DR. FRANCIS CARTER WOOD (New York): As I said this morning, the interesting part of all this work is that we are coming to standard methods of radiation. No one has had more influence on our work than Regaud, and the reason why Regaud's work is so good is that he has based it entirely upon biological investigations in which he could observe accurately the changes which took place, with accurate measurements of the quantity of radiation applied. As I remember it, Kroenig and Gauss were the first to call attention to the fact that when equal doses were administered, the effects were equal. These were, however, doses administered at a fairly rapid rate, and Regaud's great contribution to our subject lies in slowing down the rate. If, for instance, you give a sufficient dose to cure a mouse tumor in the animal, you will get a severe radiation burn; if you split that dose into two or three, you can cure the tumor without damage to the skin. The reparative processes of the normal tissues, of course, are greater than those of the pathological in many instances—not always. The cases in which it is no greater are those which escape any benefit from radiation. In those in which there is a differential, there is an advantage in greatly prolonging the time, if possible, and that touches very closely Dr. Soiland's point of the institutional treatment of cancer. If we are going to treat patients with prolonged doses of radium, they must be kept under observation in hospital wards for periods of from two to three weeks, during which time the treatment is going on. It is Professor Regaud's chief complaint that he has no beds under his direct control and that he has to go to distant hospitals to follow his patients, where he can have no satisfactory supervision over them. If we are going to radiate patients with a filter of two millimeters of copper and gain the benefit of prolonged radiation, they must be hospitalized. Very few patients will stand the dosage given by Dr. Coutard and his assistants—five hours for ten consecutive days; that is beyond the endurance of most human beings. The principle is to catch the cells when they divide and to prolong the time sufficiently to get all these cells and at the same time spare the normal tissues which can regenerate more rapidly than the abnormal, owing to their greater vascularity and other qualities which we do not fully understand. Whether we will ever achieve 100 per cent with all these methods, is, of course, extremely doubtful, but every year shows a distinct gain over the previous one. However, it must always be remembered that every time a meeting of this Society has been held, someone has hoped

that some particular technic of his was better than anyone's else, and we know that these ideas and impressions are not always the best guide. The only way to advance steadily is to combine all the information we have, to compare notes as much as possible, to visit one another's laboratories and institutions, and not to remain too isolated. There are important facts to be learned in Stockholm, in London, and in Paris, and it is to be hoped that the information which is available in published records will be carried throughout the United States. I hope this may be accomplished by the new extension of the Journal of the Radiological Society which promises so much. I would like to see that Journal contain translations of the more important contributions of the French and German radiologists, which hitherto have evidently escaped the eye of many of our colleagues.

Dr. B. P. Widmann (closing): If we are to depend upon the caustic action of radiation in the treatment of deep-seated malignant disease, then obviously radiation therapy can never be considered as an ideal procedure, because adequate intensities in the deeper-seated structures cannot be attained without danger of damaging the integrity of the normal tissues. Every effort during the past year and a half has been spent in building up doses that will permit the delivery of two to three times the usual amount of treatment, and this could be done only by using extremely short wave length radiations. The principles expounded by Regaud, of the Curie Institute in Paris, are being adhered to insofar as continuing radiation over a long period of time (a total of from 8 to 10 days). We have not had an opportunity to have histological studies of enlarged lymph nodes made. We hope to be able to present some study of the tissue changes following extremely short wave length radiations in the near future. In two recent autopsies on patients with advanced pelvic cancers, Grade 4 involvements, all evidence of disease in the pelvic region had disappeared; in one case metastasis to the liver was found and in the second case no evidence of disease could be determined anywhere. In another instance a patient is still living and symptom-free following treatment for an extensive pelvic cancer causing a rectovaginal fistula. There is no proof that the better biological effects will be obtained by short wave length radiations. There is evidence to support both types of radiation, but if further progress in the treatment of advanced cancer is to depend upon the principles of radiation, then it is reasonable to assume that some means of delivering still greater quantities of radiation to the tissues must be devised. This development must naturally be along lines of using qualities of radiations that will preserve normal structures and still be elective for cancer cells.

Dr. G. E. Binkley (closing): I cannot agree with a previous speaker, because the amount of radium at our disposal is limited. Under these circumstances, radium should be used at the portals of entry which allow the greatest dosage at the site of the tumor, and high voltage roentgen rays, which are available in unlimited amounts at a very low cost, at the portals where a smaller fraction of the skin dosage reaches the tumor mass.

Dr. Robert E. Fricke (closing): I agree with Dr. Healy regarding the management of the cases in which there are foul and sloughing growths. It is usually more expedient to clean up the necrotic field and apply vaginal packages of radium before the intracervical or interstitial applications are started. We usually divide treatments, using the universal 50 milligram applicator or an equivalent radon tube, and a complete treatment may consist of six to eight portals over a period of two to three weeks. Between treatments, patients are permitted to

be up and about, so as to maintain or conserve their general health and strength. The best results are obtained by intensive treatment, to suit the individual needs of the patient. In the inoperable group, with health undermined, only limited treatment should be attempted; however, in a few of these cases complete treatment will be well tolerated.

DR. WILLIAM P. HEALY (closing): Dr. Swanberg and Dr. Wood are both correct in their conclusion from my paper. We formerly treated all our cases with radium as the first application, radium *per vaginam* and the bomb, or some application against the surface, and then the radium capsules within the cervical and the uterine canal, and by burying gold filtered seeds in the outer borders of the cervical lesion. Then, ten days to three or four weeks later, depending on the amount of the constitutional and local reaction to the application of the radium, we followed that series of treatments with the X-ray cycle. However, as I stated in the latter part of my paper, we are now doing a different procedure, particularly in the 60-odd per cent of advanced cases. In those, we endeavor to precede any radium application by the high voltage X-ray cycle and the use of copious antiseptic vaginal douches. We believe it is a better procedure for that group of cases, and I am not so sure but that I shall also, in time, treat even the early or favorable cases in the same way, by giving them the X-ray cycle first.

I feel that there is room for small groups of men here and there about the country, with small amounts of radium in their possession, who are interested in the cancer problem. I feel that there is not only room, but a great necessity for such groups, and that they can treat cancer to advantage. I feel that large institutions have a wide field because of the great number of cases treated by them. They represent centers of education and instruction, because of their large endowments and their laboratory facilities for research. They are very necessary, but I feel that the treatment of cancer cases throughout the country can never be properly carried on unless individuals here and there who are interested in the subject can continue to do their work.

DR. HENRY SCHMITZ (closing): I wish to thank Dr. Pfahler for his very kind discussion. His expression of appreciation of the work presented here to-day means more to me than one may realize.

The Clinical Group 4 carcinomata differ from the Histological Group 4 carcinomata. The Clinical Group 4 carcinomata are determined by the extent of the growth; chiefly whether it has caused metastases or whether it is fixed. The Histological Group 4 carcinomata are determined by the microscope and are characterized by a high degree of anaplasia and undifferentiation. One may find a Histological Group 4 carcinoma in a Clinical Group 1.

Broders, Greenough and others influenced us to apply their findings to our cancers. The only difference is that Hueper has attempted to name the various factors which constitute the malignogram and to give a method of numerical evaluation for each one of these factors. Thus the work may be duplicated by any one familiar with pathology. The clinical grouping, also, has advantages. It gives definite indications for the method of treatment which will prove adequate; it aids in the prognosis, as one may determine the relative chance of result of treatment. Finally, it gives a definite explanation of a clearly localized, a doubtfully localized, and an advanced and terminal stage of cancer.

DR. ALBERT SOILAND (closing): I am sure you all agree that the value of these cancer symposia can hardly be overestimated.

If we come together year by year in this manner, we will certainly acquire more knowledge, learn what the other man or institution is doing, and this type of information in a subject as difficult to understand as cancer, is invaluable. Such a symposium as this contains practically all the present-day knowledge on cancer, and will prove of inestimable value to every institution of learning.

RADIOSENSITIVE TUMORS AND TUMORS THAT FIRST SHOULD BE SUBJECTED TO OPERATION[1]

By JOSEPH COLT BLOODGOOD, M.D., BALTIMORE, MARYLAND

WE are learning that it is impossible to tell, in the early stage of all tumors and local lesions, the exact diagnosis clinically, or to determine, even when a biopsy is done, whether a palpable mass or a bone lesion seen in the X-ray is radiosensitive or not. As our experience becomes larger, we are discovering that many lesions are radiosensitive. Both theoretically and practically, whether there is to be an operation or not, it is wiser to try radiation first (with certain exceptions, to be discussed), either with X-rays or with radium. I have no evidence that this initial radiation is ever harmful. More recent experience indicates that any operation which incompletely removes the tumor locally, produces conditions that make secondary radiation less valuable.

It seems possible to classify local lesions, whether clinically malignant or not, into two groups: The first, those upon which radiation should be tried first; second, those upon which complete excision, with or without biopsy, should be the operation of choice. I will discuss the first group, because there are a number of new features which, so far as I know, have not been dwelt upon by cancer students in their publications.

Palpable Lumps beneath the Skin and in the Soft Parts.—We have classed these in the laboratory under two large headings: benign connective tissue tumors and sarcoma of the soft parts. There are a few subcutaneous tumors of epithelial origin, for example, the dermoid, that occur in the same localities as the benign and malignant connective tissue tumors. However, when the lump is felt in the breast, or distinctly in the thyroid gland, it is my experience that operation, except when the tumor is distinctly clinically malignant, should be the first choice. The reasons for this will be given later.

The benign connective tissue tumors that may occur in the tissues between the skin and the bone, are different types of hemangioma and lymphangioma, of which the former is the more common, and the xanthoma the most difficult to diagnose at biopsy. Then comes the large group of fibromas, so common on the tendon sheaths, and these are often xanthomas. When situated in the abdominal wall they are called *desmoids.* As a matter of fact most of these desmoids of the abdominal wall represent different stages of myositis of the rectus muscle. The benign connective tissue cysts are simply rare types of angioma, or of traumatic origin. There is no necessity here to go further into the various types of sarcoma. The most striking feature, in our studies of some five hundred cases of sarcoma of the soft parts in the past forty years, is that recurrence followed in about one-third of the cases, and as a rule in the cases that recurred the original tumor had been small, easily accessible, and had been removed by enucleation, or shelling out, either because the operator was ignorant of the danger of doing this, or because of the fact that the tumor was near an important nerve or blood vessel. This is especially true when the mass is in or near the parotid or the facial nerve.

I have found that nerve sheath tumors, whether benign or malignant, are often radiosensitive, especially in the early stage. I feel confident that if these five hundred patients whose cases have been studied in the laboratory, had come under observation early and had received X-ray or radium radiation first, there would have been no recurrences locally perhaps, although many of

[1]Written for the Special Cancer Number of RADIOLOGY, March, 1930.

them would probably have had to be properly operated on later.

Let us briefly repeat here again the dogmatic statement which, I think, is based on sufficient evidence to justify it, that no harm is done by subjecting a subcutaneous nodule to radiation first, except when it is situated in certain localities, as in the breast and thyroid gland, where experience favors operation first. Radiosensitive tumors—with certain exceptions, one of which is the giant-cell tumor of bone—show, after a few treatments, the same immediate effect as the gumma does after intravenous therapy. It may be helpful to the reader if we here note observations already recorded on this type of tumors in all localities, with some suggestions as to a better method—as least to be tried. This means that we must mix the two groups—those which should have radiation first and those which should not.

Bone Tumors.—I have selected this group first, because the X-ray pictures the actual presence or absence and degree of bone formation and bone destruction, with and without fracture, expansion of the bone shell, etc.

I have observed radiation in every type of bone disease or bone tumor, benign and malignant. The dangers have been those common to radiation by inexperienced individuals—a superficial or deep burn. There is no necessity for this to-day. Take, for example, a bone cyst in the shaft of the humerus in a girl aged twelve. It was observed by experienced surgeons, pathologists, and roentgenologists about five years ago. It was diagnosed malignant and given intensive X-ray treatment. There followed a dermatitis and cellulitis of the skin and soft parts, with destruction of tissue and an osteomyelitis, with the formation of a sequestrum. The girl's arm to-day is almost useless.

The moment one looks at the X-ray film of a bone lesion and then completes the study of the case, one should be able to divide the diseases and tumors into three groups—distinctly malignant, borderline, and benign. If the lesion is distinctly malignant, there is the choice between immediate operation (resection or amputation), or trial of radiation first. My figures show that amputation and resection have accomplished permanent cures—in 1921, 4 per cent, in 1929, 35 per cent. Among these five-year cures by amputation there are none of the upper extremity or scapula, and of the lower extremity only up to the middle third of the femur. But in the past ten years, we have observed sarcoma in the bones of the upper extremity in which the lesion was removable by excision. Two of these cases have reached the five-year period and are well. There are no cures of sarcoma of the upper third of the femur by either amputation or radiation. I have observed one permanent cure[2] of an apparent sarcoma of the upper end of the humerus, now seven years since radiation. This was a typical example of a radiosensitive tumor, the tumor so large and so extensive that it would have had to be removed by an amputation through the shoulder joint, with a piece of clavicle, acromion, and glenoid cavity. There was a palpable soft-part tumor with little or no bone formation in it, and the shaft of the humerus showed bone destruction. It was my opinion that we could exclude any benign condition of bone. Dr. Miles A. Watkins, of Birmingham, Alabama, curetted a lesion of the middle third of the tibia and then gave radium treatment. This patient[3] has now been well for five years. In the laboratory the sections showed a round-cell sarcoma of the Ewing type.

There is recorded in my laboratory a case seen with Dr. Willis C. Campbell, of Memphis, Tennessee, in which the patient has been reported as well within the past few

[2]This case has been reported in RADIOLOGY ("What Every Radiologist should Know about Bone Tumors"), March, 1927, VIII, 195.

[3]This case has also been reported by Geschickter and Copeland in their article on the Ewing Tumor in *Archives of Surgery*, April, 1928, XVI, 807.

months. The X-ray showed a lesion of the lower end of the fibula. The section made at biopsy showed a Ewing sarcoma. There followed treatment with radium. The X-ray examination after the operation showed a complete healing of the bone lesion. There is an increasing percentage of permanent cures in sarcoma of bone, both after amputation and after radiation. No harm, therefore, occurs from trying radiation first in this group which is shown by the X-ray to be distinctly malignant. If the lesion is of the upper extremity and can not be completely removed by resection, continue radiation. If the lesion is above the middle third of the femur, continue radiation. If the lesion is resectable, in the upper extremity or scapula, or can be completely removed by amputation or resection in the lower extremity below the upper third of the femur, operation is indicated, unless there is a rapid disappearance of the palpable swelling and definite changes shown by X-ray examination.

When the diagnosis is doubtful, the part or patient should be put at rest, the involved area should be radiated, and the X-ray films should be submitted to more experienced diagnosticians. *It is safer for the patient to do this than to have a biopsy made and submit sections to a pathologist for diagnosis.* This doubtful group is on the increase. The majority of them proves to be benign. When the X-ray and other diagnostic studies allow the conclusion of a benign tumor, it is a waste of time and money to use radiation, except in the giant-cell group. I have had such success with curetting when the bone shell of the giant-cell tumor was intact that it is still my rule to operate first. When the bone shell is partially or completely destroyed, I am now trying radiation first. This tumor at first reacts in an entirely different way from a radiosensitive malignant tumor of bone. At first there is further swelling and discomfort, later the discomfort disappears and the swelling recedes. So far my observations in three cases have been unfortunate. Two examples of giant-cell tumor of the lower end of the radius subjected to thorough preoperative radiation recurred after curetting and have remained well since resection. A third one, under observation now, of a giant-cell tumor of the os calcis, has shown almost complete destruction of the already partially destroyed bone shell since its first thorough course of radiation. In the Memorial Hospital, in New York, they have had the largest number of cases and the most satisfactory results. But, if radiation is employed in the giant-cell tumor, the treatment must be carried on for one or two years. I am still rather inclined to the opinion that in cases not suitable for immediate curetting, and in all other cases in which there is not a rapid reaction to radiation, if the lesion can be removed by resection and bone transplantation, the latter should be the treatment of choice. Geschickter and Copeland reported in *Archives of Surgery*[4] that no recurrences after resection of giant-cell tumor have been observed. However, if the giant-cell tumor is in the lower end of the femur or upper end of the tibia, and too extensive for resection, radiation should be given its trial to the limit.

To repeat, more bone lesions should first be subjected to radiation. Biopsy should be reserved for the last resort and, if possible, should be followed immediately by amputation or resection. A bone tumor is a lesion which roentgenologists, pathologists, and surgeons should study together before any radical operation is done, and all three should try to keep themselves informed from our rapidly growing experience.

Nerve Sheath Tumors.—There is no positive diagnostic sign that a soft-part tumor is a nerve sheath tumor, except its location near a large nerve, especially if it is situated in the popliteal space, or is associated with

[4] August, 1929, XIX, 169.

definite pain or some sensory nerve disturbance. There are three definite reasons why nerve sheath tumors should be subjected to radiation before operation. First, experience teaches us that they may be radiosensitive. Second, they are often multiple, and when the larger growth is removed, one may fail to see and remove the smaller growths in the neighborhood. In the third place, if the tumor has been given radiation and has not reacted, one is justified, at the operation, in removing the nerve if this is essential to the complete removal of the tumor. The proof of this is shown in a number of observations recorded in my laboratory. For example, a tumor in the right groin; removal by enucleation, in order to save the anterior crural nerve. There was very rapid recurrence. The patient was given the trial of radiation before an operative attempt in which there would have been danger of injury not only to the nerve, but to the artery and vein. The tumor disappeared; there has been no recurrence after five years.

There is a fourth reason for radiation first, as demonstrated by a case recently observed. The tumor, about the size of the end of an adult thumb, could be felt high in the axilla. When touched, there was sensory disturbance in the region of the ulnar nerve down into the little finger. Clinically, it was a nerve sheath tumor. Rather than operate at once and be forced to decide as to resection of the involved nerve in the brachial plexus, for three years this patient was treated at intervals of from three to six months by deep X-rays. The sensory disturbances remained unchanged; the size of the tumor was first slightly reduced, then quiescent, and then began to enlarge. The interesting finding at operation was this: This tumor had such a thickened capsule that we could remove it completely without injury to the surrounding nerves of the brachial plexus and vessels, and it was only necessary to resect the nerve actually involved. As we have had a very large experience in the study of the fresh gross appearance of these nerve sheath tumors, I feel confident that the thickened capsule was the result of radiation. A benign or malignant nerve sheath tumor may have such a definitely thin capsule that shelling out or enucleation will leave particles of the tumor behind—in such a case there is usually, if not always, a recurrence.

In following this rule of radiation in certain subcutaneous tumors on the supposition that they are of the nerve sheath, undoubtedly other types of benign and malignant connective tissue tumors will be radiated. No harm will be done. We have instructed the public—we shall be called upon to palpate a very large number of subcutaneous tumors in the soft parts. In many we can tell the patient that operation or treatment is not indicated until enlargement is observed. Rapid growth in such a tumor, whether of recent or old origin, is an indication for immediate radiation, and if there is not corresponding and immediate checking of the growth, or its disappearance, operation is indicated.

Angiomatous Tumors.—These are more common than nerve sheath tumors. Those in, or just beneath, the skin or mucous membrane can be diagnosed by their color. The deeper ones may give distinct compressibility on palpation. Any angioma small enough to be completely excised can receive this treatment at once if complete excision is not mutilating. All other angiomas should be given the benefit of as long a course as possible of radiation. If this fails, operate. Microscopic studies of angiomas excised after radiation demonstrate that this treatment increases the connective tissue between the blood vessels, whether capillary or not, and usually destroys the capillaries. The failure of radiation is largely due to the presence, in smaller or larger degrees, of cavernous angioma. These blood vessel spaces are too large to be influenced. When

there is a recurrence after the excision of an angioma, whether it had been previously radiated or not, radiation should be given another trial.

Tumors in the Axilla, Neck, and Groin.—These tumors, like tumors of bone, nerve sheaths, and the angiomatous tumors, are frequently radiosensitive. With few exceptions, nothing is lost by trying radiation first when there are single or multiple enlargements of the glands in these three areas. This is due to the fact that the three types of disease of the lymph glands which are malignant, are, for practical purposes, inoperable, or rather, not curable by operation. In lymphosarcoma and Hodgkin's disease, so far as we know, the nests of malignant cells begin in all the areas of lymphoid tissue throughout the body, or ultimately affect them. Lymphosarcoma is much more radiosensitive than Hodgkin's. Many cases are held five years or more. In metastatic tumors of the lymph glands from primary malignancy in an inaccessible place we cannot expect cure from resection. In cancer of the breast it is the rule to remove the lymphatic glands at the primary operation. If the glands are involved, the percentage of cures drops from 70 to 25 or less. I have no evidence that pre- or post-operative radiation improves the number of five-year cures, or protects the individual in any way. This is theoretically incorrect. However, experience of more than seven years with pre- and post-operative radiation has demonstrated that the greatest comfort is obtained by waiting for pain or definite signs of recurrence before instituting radiation. When, in cancer of the lip, the glands were involved and have been completely removed, the five-year cures fall from 100 to 50 per cent. In cancer of the tongue, with involved glands of the neck, the five-year cures fall to 10 per cent. Pre- and post-operative radiation of the neck, when there is a known cancer of the lip, tongue, or any part of the oral cavity or nasopharynx, has been disappointing. There are a few observations in which the patients have lived long enough in comfort to conclude that radiation has been distinctly valuable. It is better to depend upon the education of the people and induce more and more individuals to seek treatment before the glands are involved.

In tuberculous and non-tuberculous inflammations of the lymph glands, which are often very difficult to distinguish from leukemia, Hodgkin's disease, or metastasis, radiation does no harm, and sometimes seems beneficial. The question to settle first when a case presents itself with multiple involved glands in axilla, neck, or groin, with the involvement of one, two, or all regions, is whether a gland should be removed for diagnosis. I would advise the following procedure first: Look at the tonsils. If there is unilateral hypertrophy of one tonsil, give radiation first to the tonsil. The disappearance of this enlarged tonsil almost makes a positive diagnosis of lymphosarcoma. Now go ahead and treat all the lymphatic regions of the body. If the X-ray shows a mediastinal tumor, the diagnosis is almost certainly Hodgkin's or lymphosarcoma, and radiation is indicated at once. If there is a large mass of glands in axilla or neck, there is no objection to their complete removal—it can be performed under novocain or rectal anesthesia, and the operation is neither dangerous nor mutilating.

The same is not true of the glands in the groin. The complete excision of these glands will not cure lymphosarcoma or Hodgkin's disease: it may be justified in cancer of the penis, scrotum, or vulva. It rarely cures. This complete operation leaves a wound that never heals *per primam* —always by granulation, and it is often followed by lymphedema. Many patients are made uncomfortable. So, when the lesion is in the groin, remove one gland only. If there are glands in the groin, axilla, and neck, and a gland is removed from any of

these regions, and found to be microscopically negative for malignant disease, remove glands from the other two regions before concluding that the disease is not malignant. It is my opinion that unless the section of the gland shows definite tubercles of tuberculosis, or many and definite germinal centers without any foreign cells, it is wiser to give it the benefit of radiation, even if the section shows no positive evidence of lymphosarcoma, Hodgkin's, or metastasis.

The mistake we make in radiation for lymphosarcoma and Hodgkin's is that we limit it to the area involved. Should the lymphosarcoma be associated with leukemia, radiate all the skeleton and observe the effect on the leukocytes.

Male Breast.—One evening, a first-year medical student, aged twenty-two, asked me to palpate a small enlargement of the left breast which annoyed him, both from the pressure of his clothing and because his companions joked him about it in the shower-room. It had been present for three years. There were no signs of malignancy. The left breast was simply larger than the right. It had all the appearance of the so-called diffuse hypertrophy of the male breast, which as a rule becomes bilateral within six months to a year. But when males consult physicians for an enlargement of one breast during the cancer age, it is dangerous to wait for the positive signs of benignancy—bilateral enlargement. So far as I know, these breasts have not been tested as to their radiosensitivity. It is the first opportunity I have had in three years to see such a case. I may be able to report on it later.

Female Breast.—I have recorded my experience in this domain on a number of occasions, and it has also been published in RADIOLOGY. My position differs somewhat from that of my colleagues, except Robert Greenough of Boston. I have had seven years' experience with pre-operative and post-operative X-ray treatment for breast lesions. I have given up post-operative radiation in all operable cases, whether or not the glands in the axilla are involved. I know, from statistical studies covering more than forty years, that when the glands are not involved, the probability of a five-year cure after operation is 70 per cent, and when the glands are involved microscopically, the percentages vary as follows: base glands 25 per cent; mid-glands 20 per cent; apex glands 10 per cent. If borderline tumors in which there is never metastasis to glands are included, the five-year cures in this group jump from 70 to 85 per cent. One can see at once how difficult—how impossible—it would be to estimate the value of pre- or post-operative radiation, or of both, in this group, unless the pathologic reports were accurate—not only as to the malignancy of the tumor, but as to the actual glandular involvement. Comparing this group, during seven years' study, with similar cases before and since, I can find no difference in the actual percentage of five-year cures. During these seven years, in addition to pre- and post-operative radiation, we employed, when the cancer of the breast was extensive, the cautery or the electric needle, known as endothermy or diathermy. Recently we have even given these up. This does not mean that we have given up radiation in cancer of the breast, but we reserve it for those cases in which there are signs of metastasis before or after operation. Its greatest value is in the relief of pain, especially in metastasis to the region of the vertebræ. Every now and then we encounter almost miraculous results. I have never seen a verified cancer in the breast show very much radiosensitivity.

At this time I have sufficient evidence to enable me to state that chronic cystic mastitis shows the same percentage of spontaneous recoveries, whether treated with radiation or not, and that pain in the breast and discharge from the nipple are not affected by radiation with X-rays or radium. I wish

there were space and time to record here in greater detail exactly what has been accomplished by radiation for benign and malignant lesions of the breast. It can not be compared with the results obtained—and now well recognized and conceded—in cancer of the cervix and bleeding myoma of the uterus, and the value of checking the menstrual periods in older women on definite indications. Breast tumors, on the whole, are very slightly radiosensitive. In my own clinic, among every hundred women who seek advice because of some trouble or a lump in a breast, more than 65 per cent are not operated on. Much more than one-half of these breasts are lumpy. The most common pathologic process is chronic cystic mastitis, a condition which tends to spontaneous resolution. If all cases were subjected to radiation, one would erroneously conclude that there is a large number of radiosensitive tumors. Of the 35 per cent subjected to operation, more than 50 per cent are benign. If all definite lumps were radiated, it would be found that practically none of the benign lumps would show much change in the first two weeks, while many of the malignant lumps would show at least temporary decrease in size. If the observer decided to operate and used radiosensitivity for an indication, the indicated operation would be delayed in the most important group—that of cancer. Many of us, therefore, are waiting for the reports of the results of the treatment of lumps of the breast by radium alone in the hospitals of London and elsewhere.

When the lesion of the breast is clinically malignant and very extensive, it would seem best, and even definitely indicated, to try some form of radiation first; for example, in the group with skin metastasis, which is a sign that there is internal metastasis, whether it can be made out or not. Then there is a group called *cancer-en-cuirasse*. Years ago we never saw this in an operable case. Now I see, perhaps, one case out of every hundred, while it is still operable, even without glandular involvement. These cases have been given the most intensive and prolonged pre-operative radiation—none have been cured. Pain has been relieved, skin metastasis has disappeared (to return), there has been a wonderful mental effect, because the patients think something is being done for them. It will be very instructive and helpful when we have a large series of verified cases in which we can, in a cold-blooded sort of way, compare the operative group with and without radiation, with the group treated by radiation alone. Up to the present time I feel compelled to advocate surgery in all early and operable lesions, first ascertaining the nature of the tumor from frozen sections at biopsy, saving the breast when the lesion is benign, and performing the very best possible complete operation if the lump in the breast is cancer. My experience teaches me that it is a mistake, even when the tumor is minute, early, and microscopically cancer of any type, to remove the breast only and to depend upon radiation for the possible metastasis to the glands.

Paget's Disease of the Nipple.—I have published numerous statements, especially since 1921, concerning Paget's cancer of the nipple, and the treatment of the lesions of the nipple that are not cancer, but which may precede cancer. These can often be cured by simple cleanliness—frequent and thorough washing of the nipple with soap and water followed by alcohol, then covering with vaseline and protecting with a piece of gauze fixed by adhesive straps. There seems to be ample evidence that an irritation of the nipple in a woman over thirty, not nursing a child, has, if neglected, the same relation to cancer as the irritation of the nipple of a nursing mother has to mastitis. Both seem preventable diseases. Prevention comes with cleanliness and protection. It is the rule of the clinic to give these cases of irritation of the nipple, of whatever type, two or three weeks' trial of this treatment.

When there is no improvement, the patient goes to the hospital and is prepared for the complete operation. The nipple is excised under local anesthesia. If the frozen section shows malignancy, the complete operation is performed: if not, the breast is saved. Removal of the nipple and saving the breast is less mutilating and requires a less extensive operation than removing the breast and leaving the nipple.

I have had the opportunity to observe irritation of the nipple which failed to clear up when treated by X-rays or radium, yet returned to normal after treatment with soap and water. In the cases which were not affected by either, the exploratory excision of the nipple disclosed a benign or a malignant tumor. At the present moment it seems dangerous to try radiation for irritation of the nipple, as it may put off the operation when the lesion is malignant. One can be quite sure that soap and water will have very little effect on a malignant lesion. Unfortunately most forms of malignant disease are slightly radiosensitive and show temporary improvement and for this reason put off the necessary operation. If the patient wishes to run the risk in an irritation or ulcer of the nipple, I employ radiation when soap and water have failed. Of course, it can be tried first. It should be stated here that cancer of the nipple of the Paget type, without involvement of the deeper ducts or breast, may metastasize to the axilla.

Irritations of the Skin.—There are on the skin in any part of the body isolated areas of irritation, not unlike Paget's disease of the nipple. The most common is included under the term *keratosis,* which is microscopically a wart or an area of hypertrophied epidermis. Some are better described as scaly areas, like psoriasis; others are minute ulcers covered with a scab. There may be multiple areas of this kind, most commonly seen in the hairy parts. Then there is the little furuncle and the fever blister, and the single hair-follicle infection. In the past five years I have had a huge experience with such areas, in the treatment of which I have followed the same line as for irritated nipple. If the lesion does not disappear quickly under soap and water, it is completely excised under local anesthesia, with the knife, cautery, or endothermy, according to size and location. It is surprising how frequently we find microscopic areas of beginning cancer, especially of the basal-cell type. Undoubtedly many of these areas, even the malignant, have been permanently cured by radiation, but as I have seen recurrences in this type not cured by radiation and yet permanently cured by excision, I believe proper surgery, checked at operation by frozen sections, promises greater certainty of a cure than any other method. It is impossible to differentiate a small area of hair-follicle infection from a basal-cell cancer. In the early stage there is no difference between the basal-cell and the spindle-cell cancer. It is well known that the basal-cell cancer is radiosensitive, and the spindle-cell cancer very much less so. The spindle-cell cancer of the mucous membrane, especially of the mouth, is more radiosensitive than the corresponding lesion of the skin. Most of the reports on early and small skin cancer claim 75 per cent of cures. Of course, some of these are not cancer—the majority are probably basal-cell cancers. My records show that complete excision checked by frozen sections to bring out not only the pathology, but also the margin, should never fail to cure. In recurrent lesions of the skin in which complete excision would be mutilating or impossible, the results in basal-cell cancer are almost miraculous, but the more scar tissue from previous treatment of any type, the less the probability of a permanent cure. When we educate individuals to report the moment they notice an irritation of the skin, and teach the people the necessity for care and cleanliness of the skin, it is my opinion that excision will be the operation of choice in early operable

lesions. But at the present time, due to ignorance and neglect and faulty first treatment, there is a very large number of recurrent cases in which radiation with and without the cautery, coagulation, or endothermy offers the only hope of permanent relief. These cases have locally passed the stage of excision, or complete excision means so much mutilation that radiation should be tried first.

Tumors of the Skin.—Definite tumors of the skin—moles, pigmented or not; fibroma molluscum, pigmented or not; nevi and angiomas of the size and shape of moles and warts; warts; subepidermal nodules which can be completely excised without mutilation—all of these are best removed by surgery. Nothing is gained by radiation. With the exception of the angiomatous tumors and some warts, none are radiosensitive. It is really more economical, safer, and—although this statement will be challenged—no more disfiguring than successful removal by radiation. There is no harm, so far as I know, in trying radiation first. With the exception of the pigmented mole, there is no danger in delay. The danger in pigmented moles is that malignancy and metastasis occur almost simultaneously, so that when a patient notices the enlargement of a mole, or weeping, not a moment should be lost in getting rid of the local growth. The metastasis from a malignant mole is rarely, if ever, influenced by radiation; nevertheless, it should be tried, as this is the only treatment that offers anything. The attitude, therefore, to the visible, palpable lesion of the skin is entirely different from the attitude toward the invisible and palpable tumor in the soft parts which I have discussed in the beginning of this paper.

THE CONTRIBUTIONS OF EXPERIMENTAL STUDIES TO RADIOTHERAPY

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ALL the earlier radiotherapy, both with radium and X-ray, was worked out solely on a rule of thumb basis. The reasons for and the conditions of filtration, both with radium and X-ray, were but little understood, and the quantity of radiation necessary to be effective was also practically a matter of guesswork. No studies were in existence at that time concerning the relation between morphology and sensitivity. The first change in this situation was due to the work of Kroenig, Gauss, and Friedrich. The important monograph which they published in 1913 contained an immense amount of valuable experimental work done both on human beings and on biological material, such as tadpoles and frogs' eggs. At that time the conditions of measurement of X-ray and radium were rather crude, but important principles were laid down, one of which was that the effect of X-ray was independent of the wave length. The inverse square law was shown to apply, and the factor of time multiplied by intensity was shown to be true over a considerable period; that is, the results are the same when the intensity of the dose is varied in a proportion of 1:8, providing the time is equally increased. Shortly after this Wood and Prime, from the Crocker Laboratory, showed that with radium at a constant distance the equation of the lethal curve plotted with the percentage of takes of tumor particles as ordinates, and time as abscissæ was a simple curve of the pressure-volume type, provided the intensity remained the same. These writers also showed that there is a threshold below which no effect is obtained. The observations were made on both beta and gamma rays together, and also for gamma rays alone. They showed that there is no temperature coefficient observable with tumor cells between incubator temperatures, room temperatures, and 0° C. In other words, they demonstrated that a small quantity of radium over a longer period was fully equivalent to a larger quantity over a shorter period, and this was done on tumor particles. An interesting by-product of this observation was that the tumor after cultivation in animals for a period of thirteen years showed exactly the same death-point with the same radium set-up as it did at the time of the original experiments in the years 1913-14. The large number of tumor particles used and the large number of animals employed rendered the opinion of Wood and Prime unassailable from the statistical standpoint, at least as regards the exposure of tumor particles *in vitro*. The experiments were much more extensive than those of Kroenig and Gauss and confirmed on a different biological material the latters' results in every respect. Attention was called by Wood and Prime at that time to the fact that very large doses of radiation were required to destroy all the living tumor cells; in other words, to prevent growth after re-inoculation into a normal animal. During the War, Wood and Prime continued their work with X-ray, using as a means of measurement an open ionization chamber of the type originally devised by Perrin and improved by Duane. Their work was rendered much more accurate by the construction and employment of an apparatus giving a continuous current of X-ray. Under the conditions of generation of this X-ray the voltage and current through the tube could be very accurately determined and continuous readings could be made by the ionization chamber, using a sensitive galvanometer. All of these X-ray

experiments were done with particles suspended on thin gauze so as to avoid any scatter factor.

The publication of the doses of X-ray required to kill all the cells of a tumor was immediately challenged by all practical workers with X-ray. At the same time some very naive experiments were done in Germany by Kok, Keysser and others, in which tumor particles were exposed and injected into a few animals. Nothing was known about the percentage of takes of these tumors; they had not been under careful observation for any period of time; the measurements of the X-ray were very carelessly made, and the announcement was published that it was impossible to kill animal cancer cells with X-ray, while at the same time these writers were assuring the public that they could cure human cancers with very much smaller doses. The practical man resented the statement that five erythema doses are required to kill all the cells of a tumor, pointing out that he was obtaining clinical cures on rare occasions with smaller doses. Even those whose position warranted their being considered as authorities on the subject said that if these doses were correct, all effective radiotherapy would be impossible.

The last few years have done much to clear up the situation. Despite the fact that Wood and Prime called attention to the dosage being without scatter, and that scatter increased the dose, depending somewhat on the wave length (as much as 50 per cent), the importance of the scatter factor was not appreciated. Nor was it appreciated that a clinical cure can be obtained without destroying all the cells of a tumor. The study of late recurrences following apparent radiation cures and the examination of biopsy material removed from healed basal-celled tumors reveal only too often the presence of viable cancer cells. The occasional unfortunate results which have followed the removal of the uterus after a prolonged remission following radium treatment has also emphasized the fact that viable cancer cells may remain in the scarred tissues and be released to cause the death of the patient where surgery is undertaken even three to five years after the disappearance of the growth. The utter ineffectiveness of radiation in certain types of tumors has forced the recognition of the facts which were long since published on animal tumors, that is, that many of the human tumors require from five to ten erythemas to destroy all the cells and prevent recurrence. The spectacular results which have been obtained with the basal-celled tumors of the face and the carcinomas of the cervix are due in large part to the radiosensitivity of the cells in these regions. Most of the types of cancer require very much larger doses and their curability is consequently considerably less and can be achieved only under favorable conditions and with the administration of enormous quantities of radiation. The technic of this administration has become just as difficult and as complex as that of high grade surgery. Studies made on tumors of the cervix, and the fact that the squamous-cell tumors of the skin are very much more sensitive than the basal-celled type, call attention to the importance of morphology as in some sense giving a clue to the biological qualities of the cells themselves.

The introduction of grading by Broders, of the Mayo Clinic, caught the fancy of the surgeon and the radiologist, and a great deal of study has been done in attempting to correlate morphology with radiation sensitiveness. This was never Broders' original intention. He was grading on the basis of surgical cures—a very different question. Despite a large amount of work, there is considerable evidence that morphology does not give a very accurate measure of the radiation sensitivity of a tumor. In other words, as Woglom showed years ago, a mouse may have three breast tumors, all of

the same morphology, but these tumors may have a vastly differing biological malignancy, as measured by the percentage of successful inoculations. Out of all the confusion we can safely say to-day only that basal-celled tumors of the skin are sensitive, that the squamous-cell tumors are resistent, while the mixed types lie between, and that the most malignant and least differentiated cervical tumors are those which are most sensitive to radiation, while in general highly differentiated epithelial tumors are not especially sensitive. Nevertheless, in some regions, as Regaud has shown, a successful attack can be made on epidermoid carcinomata of the tongue, cheek, lip, and larynx, but as yet these results are far from controlling effectively cancer in these localities.

The next step was to determine the relation between wave length and lethal effect. Most of the papers have come from the Crocker Laboratory. Wood and his associate, Packard, have published a series of papers, Wood using animal tumors, and Packard the eggs of the fruit fly *Drosophila,* with the result that with an accurately measured, continuous current, the lethal effect is independent of the wave length, provided that the X-ray measurements are made with an open ionization chamber. The original results were obtained for tumor cells. Packard immediately repeated the work on *Drosophila* eggs and found that the same law held. He has since repeated these experiments with the gamma rays of radium and with the Bucky long wave length "Grenz" rays, and finds that the curve of killing of the *Drosophila* eggs is exactly the same with all three lengths. In the case of radium, only gamma rays were used, the filtration being 3 mm. lead. It is impossible to obtain quantitative measurements on these gamma rays in terms of roentgen units, so that a quantitative demonstration of the equality of these wave lengths has not been obtained. The form of the curve, however, is the same, and the dosage as estimated by erythema on the human skin is also nearly the same with X-rays and with the radium used. However, until it is possible to measure the gamma rays of radium and the X-rays, both in terms of the same unit, it will not be possible to show that the extremely short gamma rays are quantitatively the same as the X-rays in their biological effect. The laws governing the rate of killing which are expressed in the curves which Packard has published are, however, exactly the same. None of the small ionization chambers which are used for dosage measurement can be calibrated in terms of roentgen units, and then applied to the measurement of radium, and while it is probably true that the doses measured are in the same units, it has not been proved, because we have no way of measuring the very faint radiations from radium in an open chamber. Because a chamber is independent of the wave length from 0.6 to 0.2 Å., it is a pure assumption to state that it is also independent of the wave length 0.05 Å. Such accurate comparative measurements await the development of more sensitive apparatus but it is one of the fundamental problems in radiation measurement. The final problem is the determination of the relation between the energy of X-rays or gamma rays absorbed in the tissues and that absorbed in the ionization chamber; in other words, does the open ionization chamber measure the energy of the X-ray beam or does it not? When that is determined, we will know whether the destructive effect of radiation rests solely on the amount absorbed. No physicist will deny that in all probability it is only that absorbed which is effective, and that the effect is directly proportional to the amount of radiation absorbed, but the proof is still lacking. Interesting confirmations of these experiments of Wood's and Packard's on tumor cells and *Drosophila* eggs have been obtained by Fricke and Morse using hemoglobin solutions and certain iron salts. Independence of the wave length was observed

under these conditions. Packard has also made quantitative observations on scatter, using *Drosophila* eggs as the biological material, and shows that the published curves obtained by the ionization measurements are practically the same as those obtained by biological measurements. This adds biological proof to the fact that these curves can be used in practical radiation. The problem of the accurate measurement of X-ray and radium radiation is thus rapidly approaching solution. A rugged, simple, and cheap measuring apparatus, calibrated in biological units, has not yet been produced by the manufacturers, but this is only a question of time.

The last great biological problem which is still untouched is to determine how these rays, which act upon the atoms and not upon the molecules of the tissues, bring about the destructive effects which we observe. It is probable that such effects are due solely to the electrons which are set free in the tissues as the rays pass through, but just how such electron effects can be explained, whether by setting free of immense quantities of heat in a small area, as Dessauer has suggested, or just what the mechanism is, is still wholly unknown. However important this may be from the point of view of pure science, it is for practical therapy a relatively unimportant question. After all, the treatment of the patient will be based upon experience, and so long as radiation dosage can be measured with some accuracy, the clinical results will increase in effectiveness with the increase in the number of patients radiated under carefully controlled conditions. Advance in the future then will be largely in the hands of the clinicians, but this does not mean that the slipshod, optimistic statements of the recent past will be accepted as good coin. The radiologist must apply to his clinical data the same criteria that the surgeons have been doing. No case can be cited in evidence unless a biopsy has proved the presence of a neoplasm. The five-year period of observation must be universally adopted, and a much greater frankness than has existed hitherto must be exercised toward the failures which occur not only with radiation but with every other form of treatment in one of the worst diseases which afflict mankind.

ROENTGEN DIAGNOSIS AND TREATMENT OF THYMOMATA[1]

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PRIMARY tumors of the thymus, as a group, have not been recognized clinically in as large numbers, in the past, as they should have been if all the diagnostic measures had been employed. A perusal of the literature of this subject discloses the fact that a large percentage of the cases came to the autopsy table without a correct diagnosis having been made and many of the cases had not even had a roentgenographic study of the chest. Much of the literature is concerned with discussion of the pathology of these tumors, especially as to the origin of the small lymphocyte-like cells found in the parenchyma. This uncertainty as to the exact origin of these cells has led to the word "thymoma" being employed to designate certain tumors which in general resemble lymphosarcomata.

These tumors are relatively uncommon but apparently not so rare as the literature would indicate. Approximately one hundred cases of primary thymic tumors have been reported, of which less than twenty were carcinomata and practically all the remainder were sarcomata.

ANATOMY

The thymus is a paired organ arising from the third bronchial clefts. It occupies the anterior and superior mediastinum and varies in size according to the age and general condition of the health. It may be so large as to fill the available space between the pleural sacs laterally, the sternum anteriorly, and the pericardium and great vessels posteriorly. On the other hand, it may be so small that it is found with difficulty at the postmortem table. Its shape is determined by its size and by the structures with which it is in intimate contact.

There is a fibrous capsule which sends septa into the substance of the gland, thus dividing it into lobules which are, in turn, subdivided into follicles. These follicles consist of medulla and cortex. The structure of the cortex resembles lymph gland structure, except that the reticulum instead of being fibrous is syncytial. The spaces of the reticulum are crowded with lymphocytes. The medulla resembles the cortex, but the reticulum is coarser and contains cell nests, the concentric corpuscles of Hassall.

PATHOLOGY

Primary thymic tumors, according to Ewing (1), may be classified as follows:

(1) Lymphosarcoma or thymoma, composed of a diffuse growth of round, polyhedral, and giant cells. The chief source of this tumor is probably the reticulum cell, but lymphocytes are often present in abundance.
(2) Carcinoma arising from the reticulum cells.
(3) To these may be added very rare and somewhat questionable cases of tumors attributed to the stroma and called spindle-cell or myxosarcoma.

When the chest is opened at the postmortem table a mass is seen occupying the region of the thymus. This may be round or triangular in shape, lying in the anterior mediastinum, and is usually yellowish or grayish in color. It may be encapsulated but is frequently adherent to the sternum and surrounding organs, and may invade the pericardium, pleura, lungs, trachea, and glands. Direct invasion is more often seen than distant metastases. Metastases below

[1]Read before the Radiological Society of North America, at the Fifteenth Annual Meeting, at Toronto, Dec. 2–6, 1929.

the diaphragm have been reported in approximately five cases previous to this, according to Herriman and Rahte (26), and the site of predilection for these abdominal metastases is the kidney (2). Bone metastases have been reported, as well as metastases to the brain and most of the other vital organs. Perforation of the chest wall has been found in at least two cases. The axillary and cervical glands are frequently found to be involved, and enlargement of these glands should call for early roentgenographic examination of the chest.

The lymphosarcomata of the thymus are described as being of two groups. The first and most common is composed of small round cells arranged diffusely or lying in groups with a delicate connective tissue framework. The blood vessels may be numerous and in some cases the cells may form sheaths about the vessels, suggesting a perithelioma. The second group gives the picture of infectious granuloma suggesting Hodgkin's disease. It is composed of lymphocytes, plasma cells, and large polyhedral cells which are apparently derived from the reticulum. The lymphocytes may be very scanty.

Ewing (1) states that on close analysis the round-cell tumors of the thymus mentioned above are different from the round-cell tumors of lymph nodes.

> "The lymphocytes are scanty. The chief cell showing mitosis is often polyhedral, with acidophile cytoplasm, vesicular nucleus, and well-developed nucleoli. They often cling to the walls of numerous small capillaries where they assume a cubical or even cylindrical form. They may produce Hassall's corpuscles. The giant-cells are of two main types: (1) pale staining reticulum cells with irregular outlines, distended with vacuoles and red cell detritus, and (2) myeloid giant-cells with opaque acidophile cytoplasm and many vesicular nuclei. These giant-cells differ from the smaller giant-cells of lymphatic Hodgkin's disease."

The carcinomata of the thymus are much rarer than the round-cell sarcomata. Brannan (16) reports that he has found only fifteen cases of undoubted carcinoma reported in the literature and to these he adds one case. He also gives a good summary of these reported cases. They are less likely to metastasize than are the carcinomata of most other areas and invade surrounding structures somewhat less actively. Foot (12) states that "the tumor is of a definitely epithelial type; its cells correspond to those of a loosely built alveolar carcinoma, but differ from them inasmuch as they are stellate and more like embryonal thymic reticulum cells, and also because they tend to form bodies that resemble thymic corpuscles more closely than the epithelial 'pearls' of an epidermoid carcinoma."

CLINICAL FINDINGS

The clinical findings vary according to the type and extent of the growth at the time the patient is first seen. Cough and hoarseness are among the earliest symptoms in many cases, and several cases are reported by Janeway (3), Jacobson (4), and others in which the condition was first diagnosed as tuberculosis. Weakness, loss of weight, and pain in the neck and chest are also prominent early symptoms. Dysphagia and a sense of pressure in the upper chest may also be complaints. Pain and tingling of the shoulder and arm are minor complaints.

Later in the course of the disease, if uninfluenced by therapy, the foregoing symptoms may become extreme and, in addition, there is frequently compression of the great vessels, with resultant venous congestion of the upper chest, neck, and head, including bulging of the eyes. Pleural and pulmonary involvement, together with hydrothorax, also may complicate the picture. Extension through the anterior chest wall is mentioned by Ewing (1) and Janeway (3). Several cases of lymphatic leukemia have been reported in conjunction with thymoma.

Enlargement of the axillary lymph nodes

is a common finding and in many cases is out of proportion to the cervical lymph node involvement. Ewing (1) says that "tumors of the axillary nodes without known origin should call for investigation of the thymus by the X-ray, especially before any operation is attempted on the axilla."

Physical examination of the chest may reveal retrosternal dullness, with clear apices and lung fields, but in many of the reported cases, and in most of our cases, the mass was not suspected from the clinical examination during the early course of the disease.

ROENTGEN FINDINGS

It is apparent that the greatest reliance in diagnosis must be based on the X-ray findings since the physical findings are not constant or reliable in these cases. The X-ray appearance, in a typical case, is characteristic and consists of a more or less circular, sharply defined, non-pulsating shadow lying just above the cardiac shadow in the position ordinarily occupied by the thymus gland. Films in the lateral position show it occupying the anterior mediastinum. It may, however, project more to one side and not be symmetrically placed and in some cases it is irregular in outline. Fluoroscopic examination is valuable in ruling out aortic aneurysm.

In some cases, especially in the advanced ones, there may be extension to the pleura or lungs, with haziness of the lung fields so that the circumscribed tumor cannot be seen. Other types of mediastinal tumors are likely to be found higher up in the mediastinum and may occupy the middle and posterior portions of the mediastinum.

Aortic aneurysm may be differentiated from this condition by the fluoroscopic finding of the characteristic aneurysmal pulsation and often by its position. The combined roentgenographic and roentgenoscopic examinations should practically always differentiate these two conditions.

Mediastinal abscess may give a shadow similar to thymoma but is not likely to lie entirely in the anterior mediastinum. This should, however, be differentiated by the clinical findings, such as history, leukocytosis, and fever.

Chronic mediastinitis sometimes is shown by a diffuse widening of the mediastinum but more often by an irregular contour revealing evidence of pleural adhesions and glandular enlargement. It sometimes shows evidence of bronchiectasis in the vicinity.

Substernal thyroid is found higher in the mediastinum and the shadow is continuous with the thyroid shadow in the neck. The patient also usually gives clinical evidence of hyperthyroidism.

Various cases have been reported in the literature (3 and 4) in which the diagnosis of tuberculosis was first made before the true condition was suspected. This should practically never occur if the patient is given the benefit of roentgenographic examination of the chest.

Lymphosarcoma and Hodgkin's, while often occupying a different position, may almost exactly duplicate the shadow produced by thymoma, and they may be rather difficult to differentiate. Hodgkin's is more likely to show invasive characteristics than is the true thymoma. Differentiation here is not of great practical importance, as radiation therapy is recognized as the best treatment for both conditions.

RADIATION THERAPY

Radiation therapy is the method of choice in the treatment of this condition for several reasons: (1) This region is almost inaccessible for any thorough operative extirpation; (2) in a large percentage of the cases the disease, when recognized, is no longer a local condition but has already metastasized to distant areas or has involved the adjacent structures by local extension;

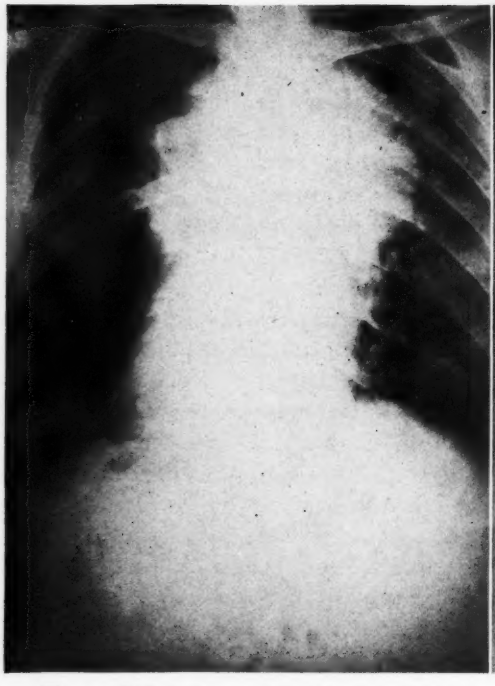

Fig. 1. Case 1. Large rounded tumor shadow before X-ray therapy (Aug. 9, 1924).

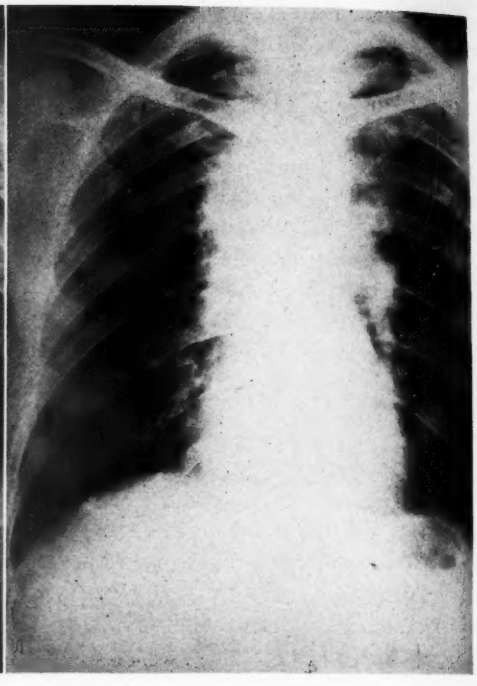

Fig. 2. Same case, showing regression of tumor after X-ray therapy (1929).

(3) these tumors are quite sensitive to radiation therapy.

The biological results from the use of X-ray and radium are for practical purposes the same, so that the problem as to the use of either largely resolves itself into a question as to the relative availability of these two methods of treatment. Unfortunately only a very few medical centers control enough radium to make therapy of the deeper structures available, while almost all hospitals and roentgenologists are equipped to give adequate X-ray therapy to this type of case. We shall confine our discussion to the roentgen method.

It has been our practice to use 185 kilovolts, 50 cm. F.S.D., 0.5 mm. of copper plus 1.0 mm. of aluminum filtration as the basic factors. The depth dose is then calculated with the aid of depth dosage charts, and an attempt is made to deliver to the tumor from 75 to 90 per cent of a skin unit dose. A similar dose is delivered to the metastases wherever found, but no attempt is made to treat the entire lymphatic system and abdominal organs, owing to the severe reactions following such treatment and to the fact that these tumors have a tendency to remain localized to the chest, axillæ, and supraclavicular areas. The lungs are shielded as much as possible to prevent fibrosis, and special attention is taken to protect the heart, as it has been shown experimentally and clinically by Hartman, Bolliger, Doub, and Smith (10) that irreparable damage may be done to the heart by excessive radiation over that organ.

The regression in size of these tumors is quite satisfactory but somewhat slower than is seen in the case of the ordinary lymphosarcoma. Entire disappearance of the tumor is frequently accomplished only after

the administration of more than one course of treatments, although it commonly regresses to a remarkable degree after a single series. Usually the shadow of the tumor mass will have decreased in size about one-half in from one month to six weeks after the first series of treatments.

There is usually some constitutional reaction, of greater or lesser degree, following intensive irradiation. This will depend upon the intensity of the irradiation, the areas treated, and the toxins absorbed from the destroyed tumor. The symptoms are much the same as in any other case of radiation sickness and vary from mild discomfort and slight nausea to extreme nausea, vomiting, aversion to food, and general prostration. These symptoms have been described more fully in a previous communication (11). A pronounced leukopenia or anemia is often produced, especially in those patients whose entire lymphatic system has been irradiated, and this may be so severe as to require repeated blood transfusions. In the ordinary case there is a return to normal in from six weeks to two months, but in extreme cases, unless blood transfusions are given, there may be a convalescence extending over many months.

Careful medical management, with special attention to reëstablishment of the normal blood level, the stimulation of the eliminatory processes, and the building up of the patient by dietary measures will contribute greatly to his general welfare.

CASE REPORTS

Case 1. C. K., male, aged 38, was admitted August 9, 1924, complaining of swollen glands in the neck and loss of 25 pounds in weight.

Physical examination revealed flatness extending to either side of the sternum, together with enlargement of the cervical, axillary, and inguinal glands.

X-ray examination of the chest disclosed a large rounded tumor mass measuring 16 cm. in diameter, extending out from either side of the mediastinum just below the clavicles. The chest was otherwise clear.

The pathological diagnosis following biopsy was: Metastatic lymphosarcoma—reticulum cell type (thymoma).

X-ray therapy was instituted immediately following this, using the following factors: 185 kilovolts, 0.75 mm. copper plus 1 mm. aluminum filtration, 50 cm. focal skin distance, 360 milliampere-minutes. In two weeks following cessation of the series of treatments there was a definite decrease in the size of the glands treated and a decrease of 3 centimeters in the width of the mediastinal tumor. In two months the superficial glands had disappeared and there was rather marked decrease in the size of the mediastinal tumor. The patient had gained 15 pounds in weight and felt in excellent health. Another course of treatments was given at that time. The patient has since that time had several relapses of the tumor, but has always responded quickly to treatment. The X-ray picture has been that of slight widening of the mediastinum, with an irregular margin. This picture in other cases has been found at postmortem examination to be associated with replacement of the tumor by fibrous tissue.

During all this time, the patient has been working, and he is quite free of symptoms at the present time.

Case 2. A. F., male, aged 39, was admitted in February, 1928, complaining of lumps in the neck. The symptoms dated back six months to a time when the patient had noticed a small gland above the right clavicle. During the past two weeks a mass had appeared beneath the middle third of the left sternomastoid muscle. There was also a mass beneath the right sternomastoid muscle which appeared to be attached to the trachea. The patient stated that it had been there for a long time, but had recently en-

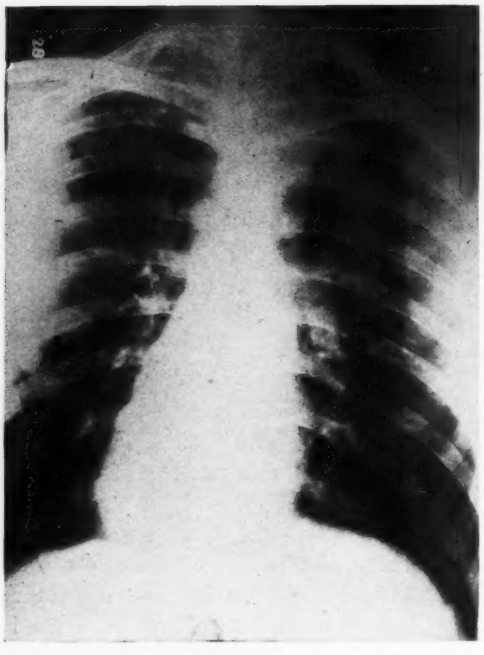

Fig. 3. Case 2. Tumor shadow in mediastinum (slightly to right).

larged and become tender. There had been a loss of eight pounds in weight.

X-ray examination of the chest revealed a tuberculous focus in the apex and subclavicular area of the left lung. There was also a shadow of increased density seen in the mediastinum slightly more to the right side, which did not project very far to either side of the mediastinum, although the margins were smooth and clear-cut.

A gland was excised from the neck for microscopical examination. Section of the gross specimen suggested Hodgkin's disease, while microscopical examination of the sections resulted in a diagnosis of thymoma, with extension to the glands of the neck.

The patient was then referred for deep X-ray therapy and, because of the respiratory embarrassment, was advised that tracheotomy might have to be done. The first series was started on February 23, 1928. The respiratory difficulty became so great that on February 27 it became necessary to do an emergency tracheotomy, which gave prompt relief. The patient continued to improve and the tracheotomy tube was removed after five months. At that time no evidence of the tumor shadow could be seen. The man has had three series of deep X-ray therapy in all and is clinically well up to the present and is taking care of his business. Repeated X-ray examinations of the chest have failed to show any evidence of return of the tumor shadow since that time.

Case 3. F. S., male, aged 25, was admitted in January, 1929, with the complaint of pain in the chest, and hemoptysis two weeks before admission. He had lost 20 pounds in weight and also had lost strength.

Physical examination suggested impairment over the left upper lobe, and a few sticky moist râles in the left second interspace near the sternum.

X-rays of the chest revealed a tumor shadow extending outwards and upwards from the left hilum area, rather suggestive of lymphoblastoma.

Because of other clinical findings, a tentative diagnosis of tuberculosis was made, but repeated sputum examinations were negative for tubercle bacilli. The patient continued to cough and to have fever, so that bronchoscopy was done. The right bronchus was found to be normal. The left bronchus was reddened and at one point there was a slight amount of grayish exudate. A lung tumor was suggested. An exploratory operation was performed and a hard rounded tumor was found at the border of the left lung. From frozen section a diagnosis of sarcoma was made. Permanent sections showed evidence of a tumor, suggesting carcinoma, and also evidence of thymic remains. Radium needles were implanted in the tumor at the time of operation and 640 milligram-hours were given with the bare platinum needles. Deep X-ray therapy was then given over the mediastinum to supplement the radium therapy.

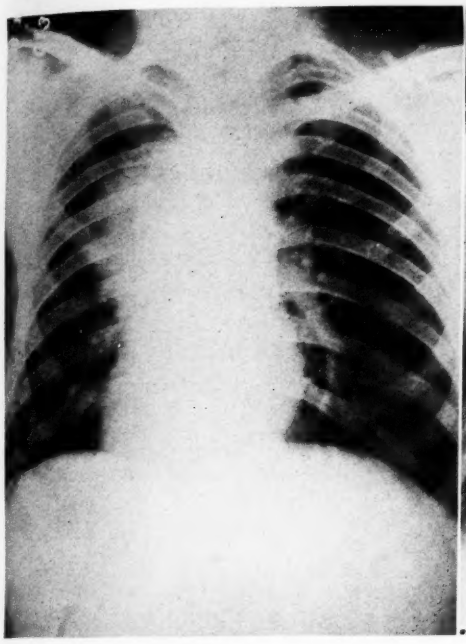

Fig. 4. Case 3. This shows a large tumor extending out from the left hilus area (Jan. 26, 1929).

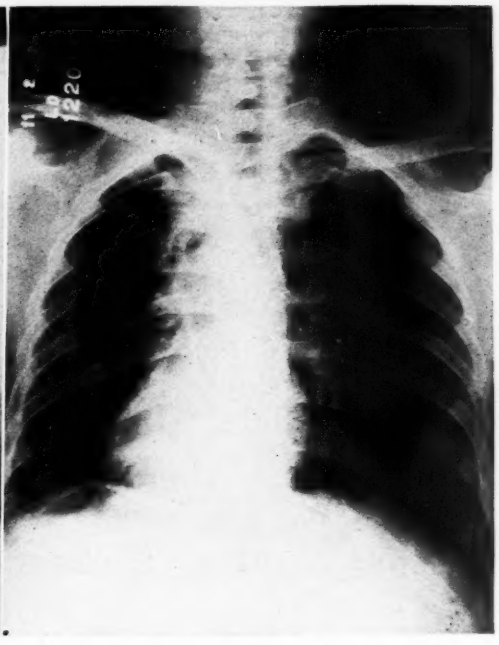

Fig. 5. Same case as Figure 4, showing almost complete disappearance of the tumor after radiation therapy (Nov. 2, 1929).

One month after this the patient had gained four and one-half pounds, was much stronger, had a good appetite, and had no chest pain. X-ray examination at this time showed very little change in the size of the tumor shadow. A second series of deep X-ray therapy was given two months after the first series. At this time the patient had gained thirteen pounds and the X-ray films of the chest showed the tumor to be about one-half of its original size. At the present time, the patient is feeling as well as usual and is able to attend to his work. X-ray examination of the chest shows fibrosis at the site of the tumor. It is impossible to state definitely if there is any tumor tissue remaining or not.

Case 4. D. G., female, aged 37, was admitted in April, 1929, complaining of cough, shortness of breath, and inability to lie on her back or right side. During the preceding six years the patient has noticed a general enlargement of the lymph glands, especially in the neck and under the arms. During the Winter of 1928-29, she was troubled by colds and a tightness of the chest. Some fluid was removed from the right pleural cavity at that time.

Physical examination revealed dullness over the right base, with restriction in the movement of the right diaphragm. There was also dullness extending laterally from the mediastinum. A mass in the abdomen lay to the right of the umbilicus. Enlarged glands were found in the right cervical area and in both axillæ.

X-ray examination of the chest revealed a large tumor shadow in the mediastinum, lying almost entirely below the clavicles and merging with the cardiac shadow below. The edges of this were clear-cut and extended almost equally to either side. There was also elevation of the right diaphragm, with infiltration of the right base and a very

small area of pneumothorax. A gland was excised from the axilla for examination. Gross section suggested lymphosarcoma. Microscopical examination resulted in the diagnosis of thymoma, granulomatous type.

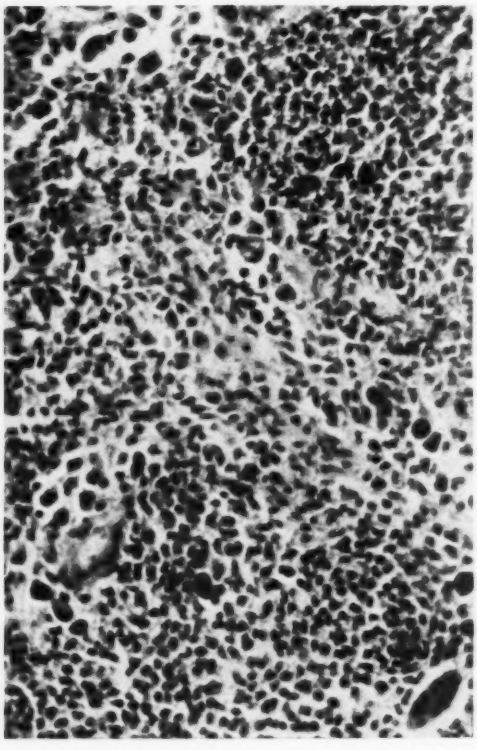

Fig. 6. Case 3. Low power microphotograph showing multinucleated tumor giant-cells, small lymphocytes, abundant stroma, and structure suggesting Hassall's corpuscles in lower left corner of the picture.

The patient was given one series of deep X-ray therapy, May 16-20, 1929. Three months later she was feeling well, was working, and had gained eight pounds. There were still a few palpable glands. At the present time she is feeling in excellent health, working every day, and complains of no untoward symptoms. X-ray examination of the chest shows very little or no widening of the mediastinum. The right base has almost entirely cleared up.

Case 5. M. H., female, aged 32, was admitted in May, 1925, complaining of fever, weakness, and loss of weight. She gave a history of hospitalization for pulmonary tuberculosis for the past three months. The temperature has been quite irregular, reaching an elevation of 105.5°. Physical examination revealed an impaired resonance over both upper lobes, together with fine crepitant râles over the same areas.

X-ray examination of the chest showed evidence of extensive pulmonary tuberculosis of both upper lobes, especially the left, also a fairly large mediastinal tumor extending out to either side of this area—a shadow which lay mostly below the clavicles and partly over the cardiac shadow.

Because of inability clinically to rule out abscess of the mediastinum, it was decided to do an exploratory examination of this under local anesthesia. This was done, and the mediastinum was entered through the sternum at the level of the second costal cartilage. A thick, firm, lobulated mass resembling thymus tissue was disclosed, a portion of which was removed for microscopical examination. This was reported by the pathologist as malignant thymoma.

One course of deep X-ray therapy was given over the mediastinum, resulting in a decrease in the width of the mediastinum. The patient then returned to her home and death occurred about two months later. No postmortem examination was made.

Case 6. B. H., female, aged 72, was admitted in March, 1927, complaining of weakness, loss of appetite and strength. Her present illness dated back six months, with weight loss of 30 pounds in that time. Recently she had had shortness of breath.

Physical examination showed an obese, elderly woman with marked tremor. There was dullness at the base of the left chest and a triangular area of dullness to the right of the spine. The heart and aorta were enlarged. There was tenderness in the epigastrium but no masses could be felt.

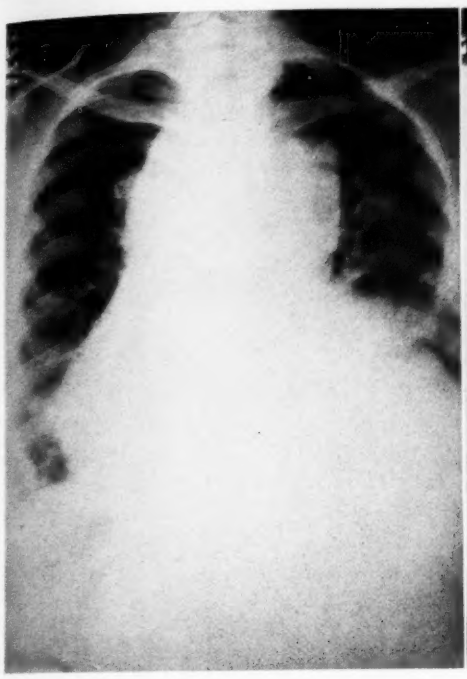

Fig. 7. Case 4. Tumor of mediastinum, with involvement of base of right lung and elevation of right diaphragm. (Before X-ray therapy, April, 1929.)

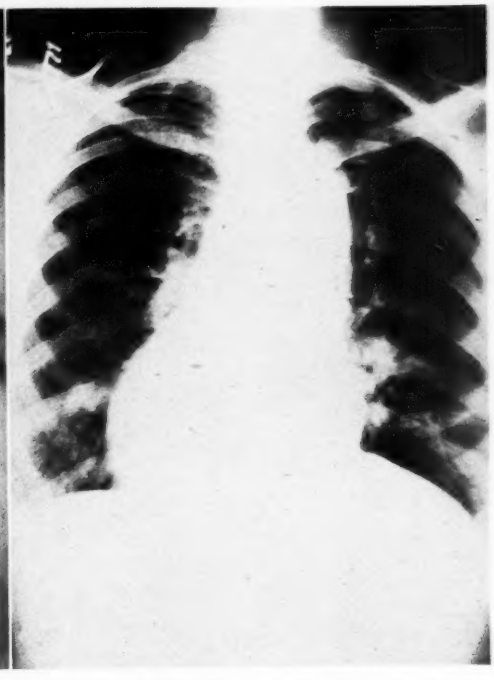

Fig. 8. Same case as Figure 7, showing regression of mediastinal tumor and clearing of right base. (After X-ray therapy, November, 1929.)

X-ray examination of the chest was made with the portable machine, but was not satisfactory owing to the patient's inability to hold her breath and to her general obesity. The films, however, did show fluid and thickened pleura in the left base and a general widening in the region of the heart and great vessels.

Fluid was removed from the left chest and microscopic examination of this showed many large cells with hyperplastic nuclei suggesting tumor cells. Fluid was again removed several days later. Death occurred from cardiac failure nine days after admission.

Postmortem examination disclosed an irregular, nodular tumor mass the size of a large orange in the upper anterior mediastinum. No thymic remains were found. The lymphoid tissue of the glands was replaced by light gray, translucent tumor tissue. Metastases to the pleura, mediastinal, mesenteric, and retroperitoneal lymph glands were found. There were also metastases to the spleen, pancreas, and peritoneum. The microscopic diagnosis was thymoma with metastases. There was also dilatation of the heart, with chronic passive congestion of the liver and spleen. The lungs showed pulmonary embolism.

DISCUSSION

In reviewing the literature one is struck by the number of cases in which the diagnosis was first made at the autopsy table. In many cases the patient had not been given the benefit of radiographic examination of the chest. Several cases are reported, however, in which the X-ray picture was not

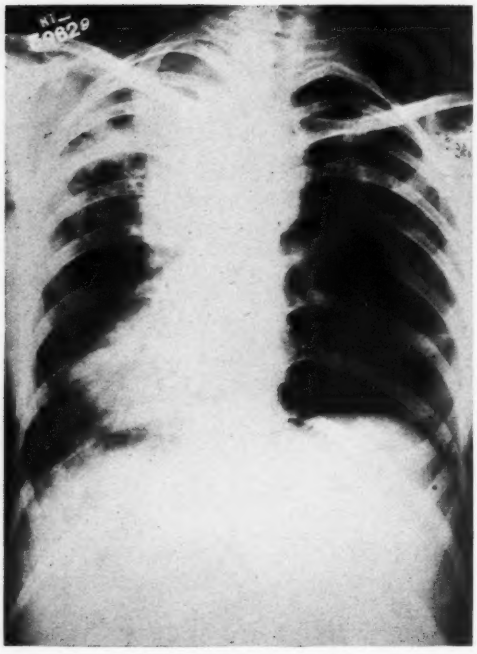

Fig. 9. Case 5. Large mediastinal tumor showing clear-cut borders. Pulmonary tuberculosis of both upper lobes.

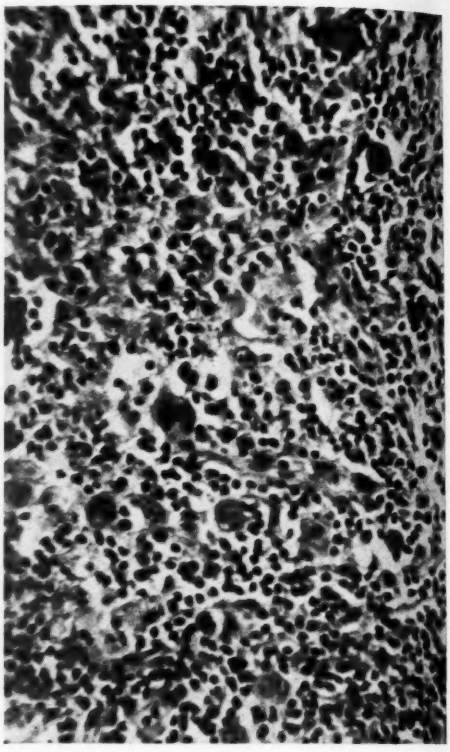

Fig. 10. Case 5. Low power microphotograph showing multinucleated tumor giant-cells, lymphocytes, and reticulum cells supported by delicate fibrous stroma.

conclusive. Jacobson (4) reported a case in which the early roentgenologic appearance suggested tuberculosis. Foot and Harrington (13) reported a case of an infant in which the tumor spread out over the left side, causing compression and destruction of the lung and producing a shadow which was interpreted as being an enlarged heart. Noice (14) reported the case of a child, aged four years, in which a pleural effusion so clouded the picture that the tumor shadow was not seen. Evert (15) reported a case in which the radiograph of the chest did not show the tumor of the mediastinum, but did show metastases through the lungs which gave the appearance of miliary tuberculosis. In Brannan's (16) case tuberculosis was first diagnosed, but shortly before death a tumor of the mediastinum was shown by the X-ray. In our cases the tumor shadow was easily made out in each case, but in several instances we were not able to state definitely the character of the tumor until microscopic examination had been done. It is apparent, therefore, that the radiographic examination of the chest is the diagnostic measure which is most apt to disclose the presence of thymomata. If the differential diagnosis can not then be made, a microscopic examination of a gland or of the original tumor should be made.

Somewhat more than a hundred cases have been reported up to date and of these approximately twenty were carcinomata. It is difficult to give the exact number owing to confusion in the terminology. Brannan (16) reviewed the literature in 1926 and found sixteen authentic cases. Several more have been reported since that date.

Symmers and Vance (17) objected to the term "thymomata" being used except in the case of those tumors which faithfully reproduce the structure of the thymus as a whole, including lymphocytes, epithelial reticulum cells, and Hassall's bodies. This name has come to be used partly because of the disagreement as to the origin of the small lymphoid cells and partly because these tumors do tend to reproduce the structure of the thymus gland and have clinical and pathological differences from lymphosarcoma of lymph glands.

Bell (18) reports a case of myasthenia gravis that had an associated tumor of the thymus, and Mella (19) states that this is a syndrome and not a disease entity. He says that the myasthenia gravis may disappear after irradiation of the thymic area.

Lymphatic leukemia has also been reported in association with thymoma. Major (20) has reported a case in which he believes the thymic condition to be evidence of disease of the lymphatic system which later manifested itself by the appearance of acute lymphatic leukemia. Friedlander and Foot (21), also Young and Spalding (22) have reported similar cases. In the latters' case the disease developed suddenly while under observation. Evans and Leucutia (23) have also reported three cases of lymphatic lymphosarcoma which terminated in lymphatic leukemia. They believe that this occurs as soon as the lymphosarcomatous involvement of the bone marrow becomes the predominating feature of the disease.

Several cases have been reported in infants and children. Renault, Cathala, and Plichet (24) reported a case of an infant aged twenty months in which death occurred from suffocation nine months after the first symptoms had been noted. Foot and Harrington (13) reported a case of an infant with an epithelial tumor, which is uncommon. They believe that this substantiates the theory that thymomata not only arise from thymic reticulum, but may present a picture that is strikingly like normal embryonic thymus at an early stage of its development.

Gandy and Piedelievre (25) reported a case which suddenly developed symptoms of obstruction of the superior vena cava. Death took place twelve days later. Harvier (7) also reported a case in which thrombosis and obstruction of the superior vena cava occurred. Foot (12) and Brannan (16) have reported cases in which death was caused by hemorrhage from invasion of a bronchus. In Brannan's case the tumor filled the lumen of the superior vena cava and closed the orifice of the azygos vein while both innominates, both jugulars, and the right subclavian veins were thrombosed. This involvement of the large vessels is one of the features that have not been stressed sufficiently.

In attempting to estimate the life expectancy of these patients who have had radiation therapy one is handicapped by the paucity of the literature on this subject. Janeway (3) reported the cases of nine patients who had had radium therapy: six of them died at intervals of from ten days to two years and five months following irradiation. The remaining three patients were alive and well at the time of the report, having received their first irradiation previously at the following intervals: (1) one month, (2) eleven months, and (3) fifteen months.

Dwyer (5) reported the case of one patient who had been treated with X-ray therapy and who was alive and in good health at the time of the report (three years later). Groover, Christie, Merritt, and Coe (6) reported two patients who had had X-ray therapy and were alive and well five and nine months, respectively, afterward. Pool (8) reported one patient who was alive ten months after X-ray therapy.

We have treated five proven cases of thymoma with X-ray therapy. One patient

received but one treatment and showed some regression of the tumor but died at home two months later. This case had extensive tuberculosis of the lungs. The other four patients are alive and well at the present time, at the following time intervals since their first treatment: (1) five years and four months; (2) one year and ten months; (3) eleven months; (4) eight months.

It is obviously too early to give any prognosis as to how permanent this benefit is going to be. However, from the uniformly good results which have been obtained from the use of X-ray therapy we believe it can be stated that these cases are quite sensitive to radiation therapy and that from its use one may expect favorable results in a high percentage of cases.

SUMMARY

1. In too large a percentage of cases in the past primary tumors of the thymus have been unrecognized before going to autopsy.

2. These cases are uncommon, but not so rare as has been thought in the past.

3. The sarcomatous type of tumor predominates but a carcinomatous type also occurs.

4. These tumors are difficult to differentiate by the ordinary clinical methods.

5. Roentgenographic examination of the chest shows this tumor as a more or less circular, sharply defined, non-pulsating mass occupying the anterior mediastinum. This method of examination is also valuable in differential diagnosis.

6. X-ray therapy is indicated in these cases as soon as the diagnosis is made. These tumors are quite sensitive to radiation therapy and prompt regression of the growth can usually be expected.

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DISCUSSION

DR. P. M. HICKEY (Ann Arbor, Michigan): I have nothing to add especially, except to report one case which we saw recently; I will read the clinical notes. The patient was a white male, five years of age, and was brought to the hospital on Nov. 11, 1929, by his mother with complaint of progressive loss of weight. The family and past histories were negative. The present illness began six weeks before admission; the child had a severe cold and coughed a great deal. The parents were not certain as to whether or not he had pneumonia at that time. He was seen by a physician, who thought the chest was filled with fluid and attempted aspiration, obtaining a small amount of bloody fluid. Since that time there had been progressive loss of weight, the child being markedly emaciated at the time of admission. An X-ray examination had been made at Albion and three attempts at paracentesis apparently failed to reveal any fluid. At this time the parents were told that the child had a tumor mass. The anterior-posterior diameter of the chest appeared to be enlarged; there was very little excursion on respiration; marked fullness and flatness over both sides anteriorly except for small areas in each base and apex. Posteriorly there was dullness over the apices, extending downward to a point opposite the point of the scapula. Breath sounds were extremely dyspneic and heart sounds were heard with great difficulty. There were a few râles in the left scapular region. Liver margin palpable 5 finger breadths below the right costal margin and extending to the left of the midline. The kidneys were palpable, enlarged and hard, particularly on the left. There was moderate adenitis in the left axillary and inguinal regions, also on both sides of the neck. The laboratory findings were as follows: hemoglobin 70 per cent; 26,000 white blood corpuscles, of which 52 per cent were polymorphonuclears, 22 per cent small and 26 per cent large lymphocytes, and some nucleated red cells. Biopsy was done of the cervical glands on Nov. 15, 1929, the findings suggesting lymphosarcoma. X-ray examinations of the chest were made on Nov. 11 and Nov. 14, 1929. I might say that the clinical diagnosis which was suggested was pericardial effusion. We made a tentative diagnosis of bilateral thymoma. This was confirmed by the biopsy on one of the enlarged glands in the neck. The child died after he had been in the hospital three or four days, and on that account therapy, which had been recommended, was not carried out. This is the appearance found both in the antero-posterior and postero-anterior positions. I would like to call your attention to this axillary line, which we were quite at a loss to explain. The lateral plate shows the shadow

Fig. 1. See discussion by P. M. Hickey, M.D., of paper by H. P. Doub, M.D.

of the tumor mass anterior to the trachea. Autopsy was performed three or four days later, after these films were made, and this mass was found to be enormously enlarged and very much infiltrated. You could make out both lobes of the thymus and also the isthmus. The shadow on one side down in the angle of the pleural cavity was found to be a string of lymphosarcomatous cells deposited in the pleura. There were lymphosarcomatous cells on the pericardium and also infiltrating both kidneys.

I think in these cases we are quite wrong if we say that the growth has its origin in the thymus. In such cases the individual has a diathesis or systemic condition in which there may be the development of lymphosarcomatous cells in any of the lymphoid tissues; if they happen to predominate in the thymus, perhaps it is not quite correct to speak of the condition as a thymoma.

Another case to which I would invite your attention is that of a young woman who had been treated for lymphoblastoma. She had a very peculiar shadow in the upper right lung field, which we were regarding as perhaps one of the manifestations of a Hodgkin's, but at autopsy there was found to be a dislocated thymus which was intensely infiltrated with these lymphosarcomatous cells.

I would like to congratulate Dr. Doub on the presentation of his paper and the very good survey he made of the literature.

Dr. George E. Pfahler (Philadelphia): Dr. Hickey's slide reminds me of a case that I have referred to as having gone through a most interesting cycle of history. Two years ago the child was eleven years of age; two years previously he had developed enlarged lymph nodes in the neck. One of them was incised, and diagnosed as a tuberculous lymph node. These nodes disappeared temporarily, but recurred, and two years after this experience, the child was brought to me with a picture almost an exact duplicate of the one Dr. Hickey has shown on the screen. I made a diagnosis of Hodgkin's disease, because there were associated some lymph nodes in the neck—not very large, probably two or at most three centimeters in diameter—and very small lymph nodes in the axilla. I gave this patient a 15 per cent dose of high voltage rays, and the child almost died. He became so ill with the rise in temperature, diarrhea, vomiting, and inability to take any food, that I called in a gastro-enterologist to help me, and it was two weeks before I could give the child any other treatment. At that time the tumors in the chest had disappeared as well as nearly all the other lymph nodes. Then the latter began to enlarge, another was taken out of the neck, sections were studied microscopically, and the diagnosis of lymphosarcoma was made. It is true the pathologist had no history — simply the specimen. We then started very slowly and with very little extra treatment over these lymph nodes, but without any success. The

child developed a progressive enlargement of the thymus, again almost to the size shown at first, followed by enlargement of the other lymph nodes, and enlargement of the liver and spleen to a degree that almost filled the abdomen. About this time he developed a typical picture of lymphatic leukemia, and died. At autopsy a diagnosis of thymoma was made, associated with lymphatic leukemia. There is a case of a child who went through the whole gamut—four diagnoses, three of them, at least, microscopic.

Dr. Lester A. Smith (Indianapolis): Recently we had quite an unusual case at the Indiana University Hospitals. According to the experience of Dr. Doub, the clinical course and the X-ray appearance of the chest are those of thymoma. While this had not been the clinical diagnosis during life, the microscopical appearance of tissue from both the mediastinal tumor and a bone metastasis was that of thymoma. The patient was a girl three years of age who entered the hospital on account of a dyspnea which had been gradually increasing over a period of two or three months. There was right exophthalmos, and left cervical and supraclavicular adenopathy had been present for two years. The first X-ray examination was not very satisfactory, the patient being almost moribund, but films made immediately after the postmortem gave clear evidence of marked changes throughout the whole shaft of one humerus, there being radiating striations perpendicular to the surface such as are found in many cases of bone sarcoma, in addition to a generalized destructive process and a pathological fracture. In several other bones, including the frontal, there was also some degree of destruction. A large mediastinal tumor was present. Reports of such bone metastases from thymoma are very rare.

Dr. Doub (closing): I am indebted to Dr. Pfahler for a very clear history of his case. This is a typical history of a number of cases which I have encountered in the literature of this subject.

In regard to Dr. Smith's case, the reason I believe it to be a thymoma is the fact that the patient had enlarged glands for two years and some difficulty in breathing. The lesion on the humerus was only incidentally found; the patient had no symptoms there which would lead one to believe they were due to a recent lesion. The fact that he found multiple bone lesions after that would indicate that they were metastatic rather than primary. The pulmonary osteo-arthropathy would also go with a long-standing chest tumor.

ROENTGEN DIAGNOSIS OF CANCER OF THE ESOPHAGUS[1]

By JOHN T. FARRELL, JR., M.D., PHILADELPHIA

THE hope of cure in malignancy lies in early recognition. Bloodgood (1) has compared the stage at which patients to-day present themselves for diagnosis of lumps in the breast with the stage at which they appeared some twenty-five years ago. In his clinic he finds that only 17 per cent of patients presenting themselves to-day for diagnosis of a lump have cancer, whereas, in the earlier period, 80 per cent had cancer, and less than 50 per cent were operable. Other observers have noted a similar increase in recent years in the incidence of benignity and operability of breast tumors (Gibbon, 2), (Klopp, 3). This change is due to increase in diagnostic acumen and to an increased popular knowledge of the course of cancer of the breast, leading patients to seek examination earlier.

This is not the case in cancer of the esophagus. Hickey (4) says that the status of the diagnosis and treatment of esophageal malignancy is an indictment of modern medicine. Jackson (5) believes that this is due in part to the physician and in part to the patient; both disregard the initial symptom, difficulty in swallowing, because of its triviality. This is unfortunate. According to Jackson (6), cancer of the esophagus is often of a mild degree of malignancy and frequently could be cured by surgery if applied early. It is essential, then, that every patient complaining of the slightest difficulty in swallowing be studied thoroughly before being dismissed as free of esophageal disease.

Roentgenology offers the most universally practicable method for the diagnosis of disease of the esophagus. While it falls short of direct esophagoscopy in accuracy, it is much simpler and more readily available. It is infinitely superior to blind bougienage, a method always dangerous, usually uninformative, and never altogether conclusive.

Roentgenologic examination of the esophagus consists in observing it fluoroscopically while its lumen contains an opaque medium. This may be done while the patient is standing or lying down: for a thorough study it must be done in both positions.

The opaque material is ingested as fluid, semi-solid or solid. Barium or bismuth salts are administered as thin watery mixtures or as thick gruels; mixed with cracker crumbs, jam, or cocoa they may be given as semi-solids; in gelatin capsules or as gelatin-impregnated blocks, after the manner of Hickey (17), they may be swallowed as solids. According to Hickey the blocks produce less discomfort when stopped than do the rigid capsules, but it is our experience that the capsules produce very little if any discomfort and that the ease with which the capsule is filled is an advantage. William H. Stewart (7) has recommended the use of sausage skins filled with opaque material. All consistencies may be employed, with the patient standing, but when he is recumbent only fluid mixtures are practical.

Standing, the left oblique is the position of choice. With the right shoulder toward the screen and the left toward the tube the patient is at such an angle that the central ray enters the body at about the left midscapular line, passes between the heart and the spine, to emerge at the right axillary line.

The right oblique prone position is the most satisfactory for examination in the horizontal plane. This has been well described by Manges (8). With the screen

[1] From the X-Ray Department, Jefferson Hospital.
Read before the Radiological Society of North America at the Fifteenth Annual Meeting, at Toronto, Dec. 2–6, 1929.

above the patient and the tube beneath the table, the patient lies with his right cheek and shoulder on the table, the right arm and hand behind, and the left leg flexed and drawn up in such a way as to rotate the body on the extended right leg and hip. In this manner the left shoulder is lifted well off the table, and with the left arm flexed the left hand can steady the drinking tube. In this position the central ray enters the chest at about the right anterior axillary line, passes behind the heart and in front of the spine, to emerge at the left posterior axillary line. By having the patient draw the opaque fluid through a drinking tube the esophagus may be filled throughout its entire length, because the flow is uphill, the introitus being appreciably lower than the hiatus.

The normal esophagus is smooth and of an almost uniform width throughout, though it does show anatomical points of narrowing (1) at the introitus; (2) in the cervico-thoracic portion where it passes from the neck into the chest; (3) at the crossing of the left bronchus, a point close to the arch of the aorta, (4) and at the hiatus. At the level of the arch it is smoothly indented on its anterior surface, and it tapers at its termination at the hiatus.

The roentgenologic appearance varies with the position of examination. When the patient is erect the opaque fluid passes readily to the stomach, pausing at the hiatus for only a second or two. A well-moistened capsule, 00 size, when swallowed in this position passes from the mouth to the stomach with only momentary delay at the points of anatomical narrowing. Hickey (17) says that a normal patient should be able to swallow comfortably a gelatin bougie 14 mm. in diameter.

It may be said that the normal esophagus does not evidence peristalsis when examined in the erect posture with fluids, though momentary delay at the hiatus is often seen in those of nervous temperament. Gentle

Fig. 1. Punched-out filling defect at the hiatus. (Patient is a male, aged 75.) After esophagoscopy, Dr. Louis H. Clerf reported a large fungating mass a short distance above the hiatus. On section, Dr. Baxter L. Crawford reported adenocarcinoma.

peristalsis is seen when semi-solid boluses are swallowed. With them, the waves mold the mass by pressure from above and force it toward the stomach, with a tapering point due to the resistance the mass meets in forcing the normally collapsed walls apart.

When examined in the prone position the esophagus is smooth, but the cervico-thoracic narrowing, the aortic indentation, and the hiatal tapering are more readily recognized because the effect of gravity is minimized. In this position peristalsis begins as a gentle wave high in the thorax and passes to the hiatus; the opaque mixture is never divided by this wave normally. During the ingestive period the opaque mixture is expelled as an almost continuous stream, with occasional accelerated spurts. In nervous individuals, the spurts are more pronounced and the mixture runs up and down the structure—a regurgitatory proc-

Fig. 2. Annular filling defect. (Patient is a male, aged 48.) On esophagoscopy, Dr. Louis H. Clerf found an extensive lesion involving the upper esophagus. On section, Dr. Baxter L. Crawford reported a squamous-cell epithelioma.

Fig. 3. Infiltrative filling defect. (Patient is a male, aged 64.) On esophagoscopy, Dr. Louis H. Clerf found a large fungating mass immediately above the hiatus. On histologic examination, Dr. Baxter L. Crawford reported a squamous-cell epithelioma.

ess—until the last of it passes into the stomach about thirty seconds after its ingestion.

Air is swallowed in varying amounts by normal individuals in the erect posture. Practically no air is swallowed when the opaque mixture is taken in the prone position through a tube.

As in other hollow viscera, the filling defect is the sign of esophageal organic disease. In the 77 cases on which this study is based it occurred in 15 instances in the upper third, in 30 in the mid-portion, and in 32 in the lower third. In all but one instance the filling defect was irregular, the character and extent of the irregularity being in a large measure associated with the site. At the hiatus it was sometimes "punched out" of a bulbous tip (Fig. 1); in the mid-portion it might be annular, when due to circumferential growths (Fig. 2), or jagged when the neoplasm was infiltrative (Fig. 3). It may be impossible to determine the exact irregularity when the lesion is high in the esophagus, because overflow into the larynx, with subsequent coughing, may prevent swallowing of a sufficient amount of the opaque fluid to outline the growth. The filling defect is quite regular in some cases of infiltrative carcinoma at the hiatus; in these, the hiatus tapers but is rigid and blunt.

Two structural changes automatically follow esophageal obstruction from any cause: (1) narrowing at the point of obstruction; (2) dilatation proximal to it (Figs. 1 and 2). Narrowing occurred in all of the 77 cases at the site of the growth. It was central when the carcinoma was annular (Fig. 2), and excentric in the

fungoid infiltrative type (Fig. 3). In lesions at the hiatus narrowing may not be pronounced because of protrusion of the growth into the cardia. Narrowing in lesions in the upper third may be so marked that it is impossible to fill out the esophagus at a lower level.

Dilatation of the proximal portion is rarely the significant finding in cancer that it is in the other esophageal lesions. It occurred in all but 4 of our patients, in 61 it was very slight, in 12 it was definitely pronounced. Three of the four cases without dilatation occurred in the lower third, the fourth was an infiltrating polypoid cancer of the middle third. Location of the lesion bears no relation to the absence of dilatation, because, in the other 29 patients, with involvement of the lower third, there was appreciable widening. Increased peristalsis is unusual in these cases. The relatively slight dilatation and the lack of increased peristalsis is probably due to the usual short course of the disease. The duration before death is too brief to permit of the marked dilatation and increased peristalsis seen in benign obstructive lesions of long standing.

Fig. 4. Lower lobe aspiration infection, with metastatic nodule complicating cancer of the upper third of the esophagus. (Patient is a male, aged 68.) Dr. Louis H. Clerf reported an extensive fungating lesion below the suprasternal notch. Dr. Baxter L. Crawford reported the tissue as squamous-cell epithelioma.

Metastasis and pulmonary infections sometimes complicate esophageal cancer. Enlargement of the mediastinal lymph nodes does not occur to any great extent in this disease. Typical metastatic nodules are sometimes seen in the lungs, but their occurrence is only occasional. In this tendency of the lesion to remain local and to metastasize late some hope of cure is seen, if the diagnosis can be made early. Metastases to other organs are sometimes found at autopsy, and in some instances enlargement of the liver or metastasis to the bones may be demonstrated roentgenographically.

Lower lobe pulmonary infection is a frequent complication of esophageal malignancy (Fig. 4). It occurs particularly when disease in the upper third produces marked narrowing; overflow into the respiratory passages brings about an aspiration infection. Roentgenographically there is a bilateral exudative increase in the lower lobe markings suggestive of bronchiectasis. The extent of the change depends upon the duration of the disease. Clinically, cough and expectoration accompany these pulmonary infections. Sometimes there is elevation of temperature.

Fistulous communication between the esophagus and trachea (Fig. 5) or the esophagus and a bronchus may follow erosion of these structures by the newgrowth. In his study of esophageal roentgenography Pancoast (9) has an illustration of a similar case.

DIFFERENTIAL DIAGNOSIS

Among the organic conditions which must be differentiated from carcinoma of

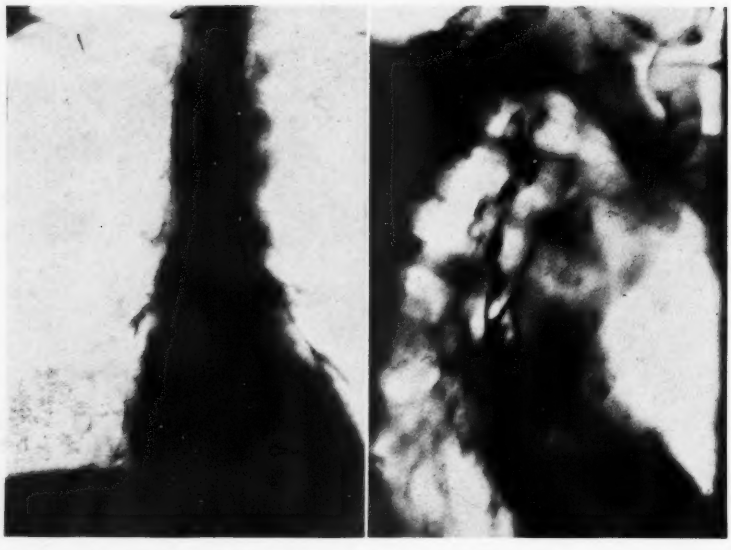

Fig. 5. Esophagotracheal fistula. (Patient is a male, aged 41.) At esophagoscopy, Dr. Edmund L. Aucoin found almost complete obstruction by an infiltrating fungating mass 26 cm. from the incisors, with dilatation of the proximal portion of the esophagus. Dr. Baxter L. Crawford reported the tissue as squamous-cell epithelioma.

the esophagus are cicatricial stenosis, stenosis from external pressure, esophageal varix, diverticulum, esophagitis, foreign body, and esophageal extension of gastric malignancy.

Phrenospasm, central nerve lesions such as bulbar palsy, and hysteria are the functional conditions with which esophageal malignancy may be confused.

Cicatricial Stenosis.—The history is important in the differentiation of this condition, seen more commonly in children than in adults. Unwitting swallowing of improperly labeled commercial lye is the most prolific source of esophageal burns (Jackson, 10), (Clerf, 11). When it is known that an acid or caustic alkali has been swallowed the diagnosis is readily made. Narrowing, the most striking roentgen characteristic, may extend throughout the length of the esophagus, or for only a few millimeters. The narrowed walls are usually smooth, and sometimes the scar is tapering in outline (Fig. 6). The degree of proximal dilatation depends upon the site of the cicatrix, its length, width, and duration. When high, there is very often no dilatation; this is also true when the entire length of the organ is involved. A localized scar in the middle or near the hiatus, with marked stenosis, may double the breadth of the proximal portion and lead to vigorous peristalsis. While dilatation and peristalsis are more marked in benign cicatricial stenosis than in cancer they never attain the proportions that they do in phrenospasm.

Stenosis from External Pressure.—Pressure from an aneurysm of the aorta, from a mediastinal newgrowth, or enlarged mediastinal lymph nodes may sometimes be confused with carcinoma of the esophagus. Aneurysm is practically always recognizable roentgenologically, and the narrowing it produces in the esophagus corresponds to its site, is smooth, and usually curved or crescentic in outline. This is also true of generalized dilatation of the aorta without aneurysm (Fig. 13).

When large enough to produce pressure, mediastinal neoplasms are usually readily recognized either fluoroscopically or on films of the chest. Dysphagia is not a common symptom of these conditions though it does sometimes occur. Deformity of the esophagus produced by mediastinal tumors is found at the site of the tumor and is smooth in contour.

The deformity due to metastatic enlargement of the mediastinal lymph nodes is similar to that of aneurysm and primary mediastinal neoplasm. Sometimes the esophagus is caught and occluded in a mass of metastatic nodes (Fig. 7). In these cases history of a remote primary growth is important.

Esophageal Varix. — Enlargement and rupture of the veins of the esophagus may lead to hematemesis (Jackson, Tucker, Clerf, Lukens, and Moore, 12). In some cases filling defects similar to cancer are observed (Fig. 8). While clinical recognition of hepatic cirrhosis may hint at the origin of the changes in the esophageal outline, direct esophagoscopy is the only way by which the condition may be differentiated from intrinsic malignancy.

Diverticulum.—In most instances a single diverticulum occurs in the upper third of the esophagus and only occasionally in the middle or lower third (Fig. 13). Sometimes the sacculation may be double; in rare instances it may be multiple, as in the case reported by Roldan (13). While difficulty in swallowing may suggest cancer, roentgen examination will readily demonstrate the characteristic pouch. Sometimes after surgical removal the dimple of the stump may retain the opaque mixture, or puckering of the wall at the site of the extirpation may suggest a filling defect (Fig. 9).

Esophagitis.—Ulceration and granulation tissue of benign origin produce constant filling defects similar to those seen in ulceration secondary to malignancy. Clinical symptoms of dysphagia, pain in the chest, and loss of weight accompany the condition. Differentiation can be made only by direct esophagoscopy, with the removal of a piece of tissue for histologic study.

Fig. 6. Esophageal stenosis due to the swallowing of a caustic. The patient, a male, aged 40, had swallowed a caustic, probably lye, twenty-one years before the present examination. At esophagoscopy, Dr. Louis H. Clerf found almost complete stenosis just above the hiatus. The walls were smooth.

Foreign Body in the Esophagus.—No difficulty is encountered when the foreign body is opaque, but with non-opaque substances the conditions may not be clear. In adults, the history is important and usually points to a foreign body. In the insane, dysphagia, with regurgitation, might lead to the clinical diagnosis of neoplasm. Clerf (14) reports the case of an insane patient in whom, because of suicidal tendencies, refusal to take food was ignored until it was observed that he was not swallowing his saliva. Ordinary roentgenograms of the neck and chest failed to reveal a foreign body, but Manges demonstrated complete obstruction to the passage of the opaque mixture

Fig. 7. Esophageal stenosis due to enlarged metastatic mediastinal lymph nodes. Dr. Frederick J. Kalteyer's patient, a female aged 54, having scirrhous carcinoma of the breast, with metastasis to the lungs and pleura. Marked relief after deep X-ray therapy given by Dr. Willis F. Manges. Dysphagia developed later, and Dr. Manges reported esophageal obstruction. On esophagoscopy, Dr. Chevalier Jackson reported pale, edematous, swollen mucosa above a tight stenosis but no evidence of ulceration.

Fig. 8. Esophageal varix. (Dr. Frederick J. Kalteyer's patient, a male, aged 58.) On esophagoscopy, Dr. Louis H. Clerf found a purplish mucosa, with definitely enlarged veins at the hiatus; no evidence of infiltration, ulceration, or external compression.

and at esophagoscopy Clerf removed a large pecan.

As Manges (15) points out, a bolus of food or other material lodged in the upper end of a stricture will produce a different type of filling defect than cancer: the opaque mixture will spread over the foreign body so that the lower border of the column is concave. In some instances a bolus may be caught in a normal esophagus and produce a similar defect in the stream (Fig. 10).

Difficult swallowing of sudden onset due to the occlusion of the esophagus by food caught at the site of malignant disease may be the first symptom of carcinoma. For this reason the esophagus should be re-examined after the esophagoscopic removal of any foreign body.

Cancer of the Cardiac Portion of the Stomach.—Gastric cancer may lead to spasm at the hiatus, or, by extending into the esophagus, produce a filling defect. In cases of phrenospasm in those past middle age the possibility of gastric cancer as the causative factor must be borne in mind (Fig. 11).

Hickey (16) recently emphasized the difficulty of diagnosing cancer of the cardia and suggested the recumbent left lateral position as being valuable in the study of patients in whom this condition is suspected.

He enumerated the roentgen signs of gastric cancer at the cardia as:

"1. Irregularity in the spurting of the barium from the esophagus into the stomach.

"2. Irregularity in the outline of the cardia in the Trendelenburg or left lateral position.

"3. Constancy of deformity in serial films.

"4. Marked gastric hypermotility."

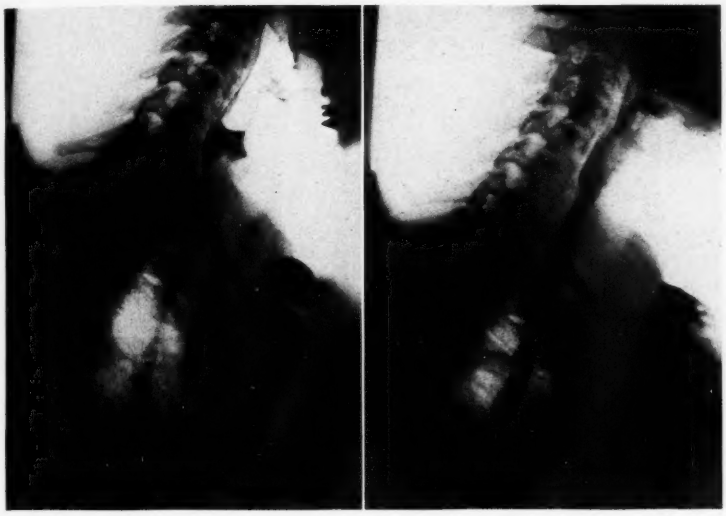

Fig. 9. Diverticulum, before and after removal. (Patient is a male, aged 58.) Surgical extirpation through the neck by Dr. Thomas A. Shallow and Dr. Louis H. Clerf. Post-operative roentgen study done during convalescence, before complete recovery.

Phrenospasm or Preventriculosis (so-called cardiospasm).—This condition is characterized clinically by many of the features of esophageal malignancy, notably dysphagia and regurgitation. Sometimes there is thoracic pain and loss of weight. Phrenospasm is distinguished by its chronic course, adults often dating the symptoms back to childhood. These patients usually come under observation at an earlier age than do those suffering from malignancy.

The roentgen appearance is striking in a pronounced case. Spasm at the lower end of the esophagus delays the opaque fluid in its passage to the stomach, the length of the delay being from a few seconds in the mild cases to hours or even days in the severe. Unlike cancer there is no filling defect, the esophagus being smooth throughout and the lower end tapering to a point. The esophagus dilates in some instances to four or five times its normal width, because of the great length of time before symptoms reach a stage requiring treatment. Peristalsis is usually vigorous. Immediately after the ingestion of the mixture deep waves may pass from the suprasternal notch to the hiatus in an attempt to force the material through. Later the waves diminish in intensity, and finally, with exhaustion of the musculature, cease altogether. The esophagus may be so filled with liquid food remnants at the time of the first examination that a considerable length of time may be required for the opaque mixture to seep through the material to the hiatus.

Lesions of the Nervous System.—Bulbar palsy, occurring as it does at the same age

Fig. 10. Foreign body (bolus of food). (Patient is a male, aged 45.) At esophagoscopy, Dr. Louis H. Clerf removed a large bolus of meat. Esophagoscopically and roentgenographically the esophagus was normal after removal of foreign body.

Fig. 11. Phrenospasm secondary to gastric malignancy. (Patient is a female, aged 62.) At esophagoscopy, Dr. Louis H. Clerf found the entire thoracic esophagus dilated but the mucosa normal except for esophagitis at the hiatus. The hiatus was smooth and showed no evidence of ulceration. Under the fluoroscope and on the film the esophagus was seen to be smooth throughout its course. A filling defect on the lesser curvature can be seen.

period as malignancy, is the most important of these. In this condition coughing and choking caused by the passage of the opaque material into the larynx may make it impossible to fill the esophagus. The esophageal stream may be so thin that one cannot rule out a massive lesion high in the esophagus. The history of regurgitation through the nose, drooling, and speech difficulties, together with the absence of demonstrable obstructive lesion, may serve to differentiate the two conditions.

In localized conditions of the nerves controlling the muscles of deglutition like difficulties may occur (Figs. 12 and 13). Esophagoscopy should be done in cases of these types in which the roentgen diagnosis is not conclusive.

Pulmonary infection of the aspiration type, similar to that seen with cancer high in the esophagus, is a common accompaniment of bulbar palsy.

Hysteria.—Patients suffering from globus hystericus and complaining of a lump in the throat due to spasm of the pharyngeal muscles are frequently referred for diagnosis. The absence of organic lesions can be readily demonstrated. Dysphagia as an accompaniment of other hysterical states is rare. When it does occur it is usually seen in young females, in contrast to esophageal cancer—a disease of males in the later age periods. When the patient can be induced to swallow, the normal condition of the esophagus becomes at once apparent.

CONCLUSIONS

1. The present status of the diagnosis and treatment of cancer of the esophagus is

unsatisfactory because of the impossibility of cure at the late stage at which these patients come under observation.

2. Even the slightest difficulty in swallowing must be investigated thoroughly before it is dismissed as inconsequential.

3. Roentgenology offers the most universally practical method for the diagnosis of diseases of the esophagus.

4. In this series of 77 cases of cancer of the esophagus the disease occurred 15 times in the upper third, 30 times in the middle, and 32 times in the lower.

5. A filling defect was observed in all patients; in but one instance was it smooth; in the other 76 it was irregular.

6. Narrowing at the site of the growth was a constant finding.

7. Slight dilatation of the proximal portion was present in 73 instances; in 4 it was absent.

8. No relationship existed between the site of the growth and the absence of dilatation.

9. Increased peristalsis is not a prominent feature of cancer of the esophagus.

10. Metastases and lower lobe pulmonary infections occur as occasional complications. Erosion of the trachea or a bronchus, with the creation of a fistulous tract, is rare.

11. The following organic lesions must be differentiated from cancer of the esophagus: cicatricial stenosis, stenosis from external pressure, esophageal varix, diverticulum, benign esophagitis, foreign body, and extension of gastric malignancy.

12. Phrenospasm, or so-called cardiospasm, central nervous system lesions such as bulbar palsy, localized lesions of the nerves controlling the muscles of swallowing, globus hystericus, and hysteria are the functional conditions which must be differentiated.

13. In all conditions in which a positive diagnosis as to the presence or absence of organic disease of the esophagus cannot be made by roentgen study, esophagoscopy should be employed.

Fig. 12. Anterior laryngeal and tracheal walls outlined by overflow. (Dr. Robert M. Lukens' patient, a female aged 72; see also Figure 13.) Overflow of the mixture into the larynx prevented proper filling of the esophagus and a diagnosis of probable newgrowth in the esophagus was made. At esophagoscopy, Dr. Lukens found the esophagus normal throughout.

I am indebted to Dr. Chevalier Jackson and the Staff of the Bronchoscopic Clinic, by whom most of the patients on which this study is based were referred, for permission to use the clinical data.

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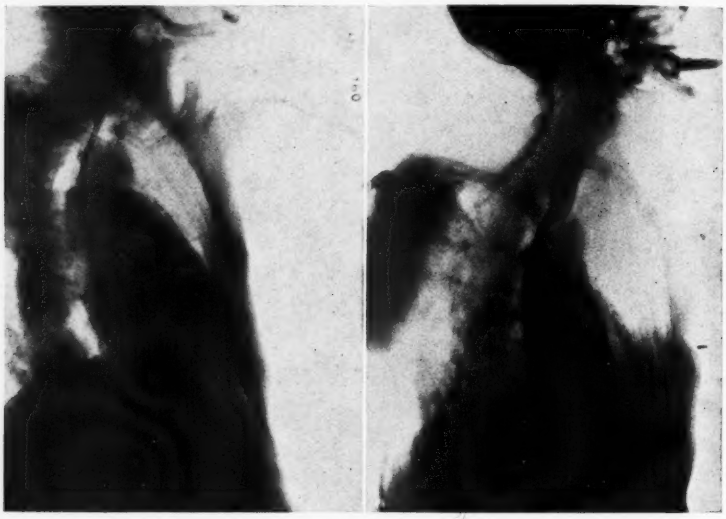

Fig. 13. Smooth indentation at the level of the arch, with a small diverticulum in the middle third, in a patient with dysphagia due to disturbance of the deglutitory muscles. (Same case as shown in Figure 12.) On the left a feeding tube passes the entire length of the esophagus; on the right the filled esophagus is shown after recovery.

DISCUSSION

DR. SYDNEY J. HAWLEY (Danville, Pa.): There are a few points which are so easily overlooked in the daily routine of our work that they should be emphasized. In the first place, we should diffuse information among the public and profession about the necessity for early examination. The examination of the esophagus is not an easy one to make, and when the patient does come for such an examination it behooves us to be very care-

ful and to examine from all directions. We must be wary about the interpretation of smoothness of outline. As Dr. Farrell mentioned in one case of carcinoma of the esophagus, the outline was smooth. On account of this fact and also because certain benign lesions are indistinguishable from early carcinomatous lesions, we must depend on the esophagoscope for the final word.

Another point which is of great importance, yet frequently omitted, is the examination of the esophagus after the removal of the foreign body. If this is carried out, you may pick up a very early lesion.

Another point of importance which Dr. Farrell brought out is that of persistent delay at the lower end of the esophagus, which may be an indication of the disease in the cardiac end of the stomach. We, as roentgenologists, should never make a diagnosis of globus hystericus: that should be left for the esophagoscope. If that reveals no signs, then the esophagoscopist may say that the difficulty in swallowing is hysterical.

Dr. Maurice Feldman (Baltimore): In a report of 128 cases of carcinoma of the stomach in our clinic, we have met with a small number of early cases of carcinoma of the esophagus. The essayist and the previous discussants have mentioned the fact that particular attention must be paid to the esophagus when there are esophageal symptoms. Now why do we have to wait until esophageal symptoms develop? Every X-ray examination of the gastro-intestinal tract requires a thorough esophageal examination. It has been my experience that if the esophagus is examined more thoroughly in the routine examination, regardless of the symptoms, we may find the earlier signs more readily.

Most of the slides shown on the screen were those of obstruction. Carcinoma with obstruction offers very little difficulty in the diagnosis. When you get obstruction, with an irregular defect, it offers little difficulty in diagnosis, but the early cases do not show signs of an obstruction. I have a slide here to show of a patient who had practically no symptoms relating to the esophagus —the only symptom this patient had was heartburn. We made an esophagoscopic examination and found a small epithelioma about the size of a pea. Peptic ulcers were also reported, following both experimental and human tests. We have never found any difficulty in differentiating peptic ulcers from carcinoma. In one case because the patient had obstructive signs, we made a diagnosis of an esophageal lesion and the esophagoscopic examination revealed a carcinoma.

Dr. A. L. Lockwood (Toronto, Canada): It is with considerable temerity that I, as a mere surgeon, appear before such an austere Society as yours, especially to discuss such a subject; because, as Will Rogers would say, from what I read in the papers, it would appear that cancer is to be removed entirely from the realm of surgery to that of radiology. There are certain types of cancer which I would be very glad to turn over to the radiologist. I would be pleased to let him have cancer of the cervix, cancer of the liver, and cancer of the esophagus.

I would not try to enlarge upon Dr. Farrell's most excellent résumé of this subject, or upon the remarks of Dr. Chevalier Jackson. If there is anyone in this world who knows anything about the subject, it should be Dr. Jackson. However, I think we should constantly keep in mind the necessity of the most meticulous and careful examination of every patient who complains of any difficulty in swallowing. No matter how slight the difficulty may seem, we cannot do too much to determine the cause.

About eight or ten years ago I had an opportunity of seeing a patient, with a very much older consultant whom you all know, a man of vast experience. As we approached the consulting-room a younger doc-

tor said to the consultant, "This is a very interesting patient, and we think he has an hysterical aphasia." The patient said that practically all his life he had had something tugging in this side of his neck. About sixteen or eighteen years ago, while drinking in a creek, something came into his throat and he choked, and it came out of his mouth and he clutched it in his fingers, but lost it. About eight or ten years later the same thing happened again. He had seen this little red thing coming out of his mouth, and he had caught it in his fingers, but it got out of his fingers again. The old consultant, who was experienced, turned the man upside down on the table and said to him, "Cough." To my surprise something red came out of his mouth and I grasped it, but lost it again. The esophagoscopic examination revealed a large tumor, fixed to the esophagus opposite the cricoid cartilage. It was removed surgically and was found to measure 11 centimeters in length and about 2 centimeters in diameter—a hemangioma.

I have just seen a woman who had been diagnosed as having hysterical aphasia. Having this other case always in mind, we examined her with an esophagoscope. A short distance down the esophagus we came to a blind pocket. If I had had the least idea that Dr. Jackson was going to be here to-day, I would have had him see this woman. I could not get even a thread down her throat. She gives a history of some sixteen years' duration and says that "when a sister was burned she got this trouble." She cannot get any solids down, and fluids only very slowly. As I said, I could not get a linen thread down her throat. We have let her go home, but will have her back again and try again to pass the esophagoscope. The esophagus tends to contract gradually to a funnel-like constriction, but we could not find an opening.

What are we going to do to help patients with cancer of the esophagus? I am convinced that the majority of them have to be left for radium or deep X-ray therapy. I have seen only one case in which I hoped to do something surgically. After experimental work on dogs, I now believe that if I had used an epithelized tube-graft the patient would be alive to-day.

As Dr. Jackson points out, the cases discovered almost by accident are the only ones which we see early enough to be able to do anything with surgically. If we are going to get anywhere as surgeons with cancer—apparently we are not, from the papers—we have to learn when to hold our hand; and that is particularly true in cancer of the esophagus. If the surgeon is to be allowed to deal at all with the esophagus, he must know when to stop. The last three cases I stopped at once after exposing the lesion, and after realizing that further surgery was not practicable. The surgeon must make it clear to the patient that he is not sure how much he can do, but that exploration will not do any harm. If the growth is too extensive, or if the surgeon does not think he is going to have a fair chance of getting a satisfactory union, preferably by an epithelized graft, he should close the incision without attempting anything further.

I think an extremely small percentage of cases would be surgical, but it would as yet seem as if they must be discovered almost by accident to be early enough to be dealt with surgically at all. If we cannot do anything surgically, what else can we do? Apart from X-ray or radium therapy, I think all we can do is by dilatation. I have seen quite a number of patients with cancer of the esophagus during the last fifteen years, yet have seen but one esophagus through which I could not get a linen thread. Undoubtedly there are such cases, and with some of them we have had to persist for some time; but if we have been able to get a linen thread through, with a metal dilator, we have been able to dilate the esophagus and get the patient back to solid or semi-solid food, or at least to fluids. If you can get even fluids

through it will relieve the situation, as these patients are intensely dehydrated. We recently had a patient, now dead, whom we dilated. He did well, so much so that he thought he was going to be cured; but he dropped dead suddenly about five months later. The letter which his wife wrote to us tells how greatly he was relieved of his intense thirst by being able to take fluids. We now have a man who has experienced this relief for about eleven months, and he came in the other day with a banana to show us how he could get even a banana down. He is now losing weight, however.

While I am about ready to turn over all cancers of the esophagus for X-ray or radium therapy, yet there may be an occasional case which will be diagnosed early enough to be available for surgery. In addition, I have not observed any benefit whatever from the use of radium or X-ray therapy.

Dr. Chevalier Jackson (Philadelphia): This presentation by Dr. Farrell is intensely interesting to me, and all the more so because I have seen a number of the patients in consultation with Dr. Farrell.

One of the most important points, I think, is that all of the diagnoses of cancer of the esophagus are late; and the reason why they are late is that the patients are not seen by either the roentgenologist or the esophagoscopist until there is difficulty in swallowing solids. We rarely see these patients in the early stages of the disease. The early stages of cancer of the esophagus are associated with such vague symptoms, and the sensations are so ill-localized by the patient, that the average practitioner makes a diagnosis of hysteria. All patients coming in with cancer of the esophagus report two forms of diagnosis: (1) spasm, and (2) hysteria, sometimes nervousness. The history of the case is absolutely worthless for diagnosis. Some patients with a history of intermittent difficulty in swallowing have had this difficulty for twenty years; whether old or recent, intermittent dysphagia in these cases is due not to spasm but to the lodgment of food which has later softened and passed on. On the other hand, many patients with cancer stoutly maintain that they never had difficulty in swallowing before to-day, yesterday, or last week. The history of the case, therefore, is worthless, because we would infer that a cancer could not be present for twenty years, nor could it develop in a day.

There are only two means of diagnosis of any esophageal disease that are worth a moment's consideration; these are roentgen-ray examination and esophagoscopy; both should be used. There are only two diseases of which the ray fails to give evidence: one is esophagitis and the other is peptic ulcer of the esophagus. In general, it may be said that roentgen-ray diagnosis of cancer of the esophagus is 98 per cent correct.

Dr. John T. Farrell, Jr. (closing): The points have been very well taken. It is important for us to remember the possibility of esophageal disease producing symptoms commonly referred to lower areas in the gastro-intestinal tract.

OSTEOGENIC TUMOR: GROWTH INJURY OF BONE AND MUSCULAR ATROPHY FOLLOWING THERAPEUTIC IRRADIATION[1]

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THE specific sensitiveness of different varieties of cells to radiation is rapidly becoming recognized as the evidence furnished by experimentation on animals is becoming known and as extensive clinical experience is daily confirming the experimental data. The variation in the relative vulnerability of different kinds of cells to roentgen and radium rays has been shown to provide a valuable means of identifying the cells in normal and pathologic tissues and even of distinguishing certain kinds of tumor. Indeed, such identification of cells by their reaction to irradiation promises to add much to our knowledge of the histogenesis, physiology, and pathology of many tissues, and especially of neoplasms. The exceptional radiosensitiveness of the small round cells which characterize the lymphoid structures and which constitute an important component of the blood, and of the seminal and follicular epithelium of the testis and ovary, respectively, is now so well known as to have become established. This is not yet true, however, concerning bone, which still is generally thought to possess a marked degree of resistance to irradiation. Many radiologists seem to regard bone as absolutely impervious to the influence of irradiation, but such an attitude does not rest on knowledge of the facts relating to the specific sensitiveness of bone. It is true that, in the adult body, the relative resistance of bone to irradiation is almost as great as that of the brain and nerve tissue, but an excessive single or total dose of roentgen or radium rays may cause injury to bone. But while adult bone can tolerate relatively large doses of radiation, the rapidly growing osseous structures of young animals are influenced deleteriously, even by small doses.

In comparison with many other tissues, experimental investigation of the radiosensitiveness of bone has been limited. This is undoubtedly due to the circumstance that the exposures incidental to radiography are insufficient to induce any alterations in such a dense and resistant tissue as bone. Indeed, even the much longer exposures to rays of shorter wave length currently employed in radiotherapy rarely cause recognizable abnormalities in bones subjected to irradiation. At least, this is the only conclusion which can be drawn from the paucity of reports of such injury, even if it is granted that such injury often may not be recognized. A brief review of the experimental and clinical evidence, therefore, may be worth while.

EXPERIMENTS ON ANIMALS

Perthes (1903) exposed the right wing only of three chicks, one day old, to 12 Holzknecht units of roentgen rays, for forty-five minutes, at a distance of 10 cm. When one of the animals was killed twelve days later, the growth of the irradiated wing was found to have been greatly retarded. Two other experiments having given similar results, Perthes deduced that roentgen rays can inhibit the division of cells, a conclusion which has since been amply substantiated.

Récamier and Tribondeau (1905) found, after exposing one side of the face of a kitten three days old to roentgen rays for sixty minutes, that the corresponding side of the skull as well as the eye failed to

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develop normally and gave an asymmetric aspect to the head; even the teeth on this side were shorter than those on the unirradiated side. Récamier (1905) exposed the right side of the head of a kitten four days old to about 3 Holzknecht units of roentgen rays of medium wave length (No. 8 Benoist) for periods of ten minutes six times in sixteen days, at the rate of three times a week. The remainder of the body was shielded from the rays by a sheet of lead. Radiodermatitis, in the form of inflammation of the labial mucosa, appeared after the third exposure, and the reaction of the skin increased during the ensuing month. The visual acuity of the right eye diminished, and the snout gradually deviated toward the right side. When, one month after the last exposure, the animal was killed, at the age of seven weeks, the right side of the skull was found underdeveloped and abnormally thin, giving the skull an asymmetric appearance. In all probability such asymmetry would have been still greater if the interval between irradiation and death had been longer. Even the teeth on the irradiated side were smaller and shorter than on the unexposed side of the face. Récamier (1906), having obtained the same results in two other kittens irradiated in the same manner, irradiated the right leg of two young chickens and again found that, while the exposed bones grew in a normal manner, such growth was distinctly retarded; the exposed bones were shorter and more slender. An attempt was made, also, to test the action of roentgen rays on mature bone by irradiating one posterior extremity of an adult rabbit. When the animal was killed one month later, a perceptible difference between the exposed and the unexposed limb could not be found. Récamier attributed the apparent failure of the rays to influence adult bone to the short interval which had elapsed since the limb had been subjected to the rays. In young chickens and frogs, he also found that the only effect of irradiation on articular cartilages was retardation in development proportional to the influence on the bones. Perceptible histologic alterations could not be found. Récamier justly concluded that irradiation, under the conditions employed, retarded the development of the articular epiphyses of bone, but did not cause any apparent microscopic changes.

Försterling (1906) also investigated the action of roentgen rays on growth by exposing to the rays thirty-four rabbits, five dogs, and two goats. In twelve young rabbits the entire body was irradiated; four died or disappeared soon after exposure. Seven of the eight remaining animals, which had been exposed once to rather soft rays for from five to twenty-nine minutes, showed general, and sometimes considerable, retardation of growth, but their health was not otherwise disturbed. All the animals died sooner or later, and death was always preceded by rapid emaciation. In two other young rabbits only half of the body was irradiated; in both animals the exposed side exhibited marked retardation of growth, and this affected the external parts of the body as well as the internal organs. The dose of rays was less than that required to cause the skin to react. In nine other animals (eight rabbits and one dog between one and a half and eleven days old) the head and one or both forelegs were irradiated for from ten to twenty minutes. Definite retardation in the growth of the exposed bones resulted, and this was accompanied by peculiar disturbances of the nervous system. In seven young rabbits and four dogs, the posterior portion of the body, or only one hind leg, was irradiated. Distinct weakness of the posterior extremity developed in most of the animals. When only one posterior extremity had been exposed to the rays the difference in growth was always striking. In two young goats only the calcaneal region of one posterior extremity was irradiated for twenty min-

utes one and four days, respectively, after birth. Six weeks later a valgus position of the exposed ankle joint developed in both animals, while the unexposed ankle remained normal. Exposure of individual extremities did not influence the general growth, but a general effect on growth almost always followed exposure of the head or of more than a certain percentage of the body. The disturbance in growth was the greater the younger the animal or the larger the dose of roentgen rays.

Krukenberg (1909) exposed to roentgen rays a well-developed, pregnant dog more than one year old; in due time three well-developed pups, two living and one dead, were born. Two hours after birth the posterior portion of one and the anterior portion of the other living pup were irradiated for fifteen minutes. Both animals appeared to develop normally for two weeks, when the hair over the exposed parts of the body began to fall. Although the pup whose posterior portion had been irradiated continued to develop normally, the other soon became unable to stand and tended to fall backward. The dog fed itself with difficulty, became irritable, and only artificial feeding prevented its death. These nervous manifestations gradually subsided, but as time went on the growth of the irradiated anterior portion of the body was greatly retarded and the visual acuity was deficient from optic atrophy. The head, eyes, shoulders, and anterior extremities were abnormally small. The development of the other dog, the posterior portion of which had been irradiated, also was retarded. The posterior half of the body was smaller and the posterior extremities shorter than normal, and this gave the dog the appearance of a hyena. Krukenberg was uncertain whether the nervous disturbances were direct results of irradiation or whether they were secondary to the retardation in growth of the bones.

Cluzet (1910) fractured the leg bones of three rabbits and six dogs under anesthesia, applied a fenestrated plaster cast, and exposed the fragments to roentgen rays filtered through 1 mm. of aluminium. At first two bones in each animal were fractured and one bone was irradiated, the other being left unexposed to serve as a control. The animals died, however. Later only one bone in each animal was broken, and a corresponding bone in another animal was broken but not irradiated, to serve as a control. In the unexposed animals, callus around the fracture appeared between the eleventh and fifteenth days, whereas in the irradiated animals callus did not appear until the eighteenth day, and in two dogs until the twenty-first and thirty-fourth days, respectively. In spite of the apparent absence of callus, the irradiated fractures united partly or completely. In another dog, irradiated before fracture, callus did not become perceptible until the one hundred and seventh day, and this only on the side away from the roentgen tube. This was taken to indicate that the rays act on the bone cells and not directly on the callus. The fact that frequent roentgenography of bones in the control animals did not delay the formation of callus was held to mean that large doses of radiation are necessary to retard the deposition of callus. Iselin and Dieterle (1910-1911) found that total irradiation of the growing body inhibits growth, but that a single exposure may stimulate growth. In young dogs the injury caused by local irradiation was the greater the younger the animal and the larger the dose of rays; larger animals were affected but little. They also observed that irradiation of a portion of the body caused general disturbances. They apparently were unable to determine whether or not the retardation of growth induced by irradiation was the result of injury to the cartilages. In discussing this communication of Iselin and Dieterle, Bloch stated that he never had found any disturbance of growth in children less than

two years old who had been irradiated for microsporia.

Cluzet and Dubreuil (1913) pursued their investigation further by fracturing and irradiating the leg bones of eight dogs, and obtained identical results. They found that, from twenty to thirty days after irradiation, the formation of callus recovered its normal rate of growth. Iselin (1913) exposed to roentgen rays the joints of mice and rats four days old, two dogs five and nine weeks old, respectively, and one calf two months old, and roentgenograms of the irradiated joints were made at frequent intervals. The growth of the exposed bones was always retarded. After small doses, Iselin noted an acceleration of growth of distant, unirradiated portions of the body, while after large doses the growth of the entire body was inhibited.

Brunner and Schwarz (1918), having exposed the head of four dogs, four days old, to small, but unspecified, doses of roentgen rays, found, after a latent period of from ten to fourteen days, increasing retardation of growth, muscular tremor, epileptiform convulsions, and at necropsy increased cerebral pressure, swelling of the brain, and in one dog hemorrhage in the fourth ventricle. Brunner and Schwarz did not describe the condition of the cranial bones, but the character and sequence of the clinical disturbances suggest that they were the results of increased intracranial pressure and that this may have been due to impaired development of the cranium. Brunner (1920) exposed only the heads of four kittens to 40 Holzknecht units of roentgen rays generated at a voltage corresponding to a spark gap of 28 cm., filtered through 3 mm. of aluminium, at a focal skin distance of 22 cm. Two of these kittens were killed by the mother, but when the two remaining kittens were examined the sutures of the skull were still gaping, whereas the skull of a control kitten was completely ossified. Similar results were obtained in dogs.

Albee (1920), in an experimental attempt to produce pseudarthrosis by repeated massive doses of roentgen rays, was unsuccessful and stated that frequent, massive irradiation of fracture, with or without loss of bone, did not inhibit the formation of callus.

Phemister (1926), assuming that the bone lesions which characterize Legg-Perthes' disease, Köhler's disease, Osgood-Schlatter's disease, and osteochondritis dissecans probably result from interruption of the circulation of the affected region, undertook to produce experimentally a focal, aseptic necrosis of bone and cartilage by inserting radium needles into the knee or into the medullary canal of the femur of dogs. The radium was left in place for from eighteen to twenty-four hours, and the animals were killed at intervals varying between forty-five and four hundred days. Phemister found that aseptic bone, made to undergo necrosis by implantation of radium, reacts differently if mechanical function is or is not exerted; that when an entire segment of the femur or humerus of a dog is destroyed, and is subsequently used for weight-bearing, the dead bone does not form a sequestrum, but is slowly replaced by ingrowing new bone; that when nonunion of a fracture prevents the injured bone from being used, the necrotic bone forms a sequestrum which is slowly absorbed; that when the adjacent bone and soft parts are injured by radium the replacement of the necrotic bone by new bone is slower than when the necrosis results from circulatory disturbance or from the use of chemicals, and that secondary infection of bone killed by radium leads to formation of sequestra regardless of function.

Wynen (1929), influenced by Regaud's conception that, under irradiation, the calcium of bone causes emission of secondary rays, bored holes in thick bone and inserted into the holes the roots of horse beans; similar roots were inserted through muscle,

and both the bone and muscle were exposed to the same dose of roentgen rays. At first the seedlings grew at the same rate, but when, after eight days, the lateral roots appeared, a striking difference was noted. Wynen found that bone absorbed more rays than muscle, and that the increased secondary radiation caused greater vascular injury in the bone because of its greater absorption. He also concluded that bone in rapidly growing organisms is more sensitive to radiation because of the relatively short life cycle of the bone cells. Wynen also investigated the production of bone necrosis by exposing the femur of guinea pigs and dogs to from 500 to 2,000 r-units at varying intervals. When the skin remained intact, he found it impossible to induce necrosis, but such necrosis always accompanied severe injury to the overlying soft parts. This led him to conclude that necrosis of bone cannot occur in the absence of mechanical injury or infection.

ANALYSIS OF EXPERIMENTAL EVIDENCE

The experiments of Perthes (1903), Récamier and Tribondeau (1905), Récamier (1905 and 1906), Försterling (1906), Krukenberg (1909), Iselin and Dieterle (1910-1911), Iselin (1913), Brunner and Schwarz (1918), and Brunner (1920) indubitably show that irradiation of young, rapidly growing animals causes more or less retardation in the growth of bones and other structures in the region exposed to the rays, and that the degree and duration of such inhibition is governed by the age of the animal and the dose of radiation. Iselin and Dieterle were the only ones to suggest that small doses may stimulate growth, but they did not submit any facts to support this assumption. The foregoing evidence also indicates that the retardation of growth is due to the direct action of the rays on the rapidly dividing cells of the epiphyses.

The investigations of Cluzet (1910) and of Cluzet and Dubreuil (1913) indicate that sufficient doses of roentgen rays do not prevent, but retard, the formation of callus around a fracture. Moreover, they showed that this effect resulted from direct influence of the rays on the bone cells, because the delay in callus formation occurred when the bone was irradiated before as well as after fracture. The fact that Albee (1920) was unable to observe such effect on the deposition of callus probably means that, in his experiments, the fractured bones did not receive a dose of radiation sufficient to inhibit the metabolic activity of the bone cells.

The experiments of Phemister (1926) and Wynen (1929) are extremely interesting and significant, because they furnish experimental proof of the soundness of the clinical and pathologic observations and of the validity of the deductions of Regaud (1922), Nageotte (1922), and Ewing (1926). The studies of Phemister with radium indicate the fundamental influence of mechanical function and infection on the reaction of bone to irradiation. In the absence of infection, bone devitalized by exposure to radium, but used for weight-bearing, does not detach itself from adjacent living tissues as a sequestrum, but is slowly replaced by ingrowing new bone. When, on the contrary, mechanical function is prevented by fracture, the devitalized bone separates as a sequestrum which is slowly absorbed. Impairment of the circulation of the soft parts overlying the necrotic bone delays its replacement by new bone. Secondary infection of bone killed by irradiation leads to sequestrum formation regardless of function.

CLINICAL CONSIDERATIONS

Regaud (1922) observed that large doses of radiation to an ulcerated epithelioma which has invaded the bone produces

peculiar necrosis of the bone, with complex lesions. He described two cases: one with an epithelioma of the skin and extension to the superior maxillary bone; the other with an epithelioma of the buccal mucosa and extension to the inferior maxilla. In both, the neoplasm improved considerably after repeated roentgen irradiation, but later infection developed, and this was followed by extensive necrosis of the bone, but the dead bone did not separate as a sequestrum. Such necrosis, in the many cases he had seen, always occurred in the bones of the head, secondary infection was always present, and the affected bone did not tend to separate from the adjacent living tissue. There was extremely slow, if any, tendency to formation of sequestra. Pursuing the subject further, Regaud (1922) reported that, in three cases with carcinoma of the tongue but without malignant invasion of the bone, in which radium had been applied to the floor of the mouth, against the mandible, ulceration and necrosis of the mucosa and bone occurred. He expressed the opinion, based on clinical observation, that ulceration of the mucosa inevitably leads to secondary infection, to which necrosis of the bone is due. He thought that the calcium of the irradiated bone emits secondary rays, which are easily absorbed and are very caustic. Irradiation was held to devitalize the bone and to render it a ready prey to infection, but the condition of the bone remained latent until infection caused active necrosis. The perspicacity of this observation was made obvious by Nageotte (1922), who examined Regaud's specimens. She found that, besides the death of cells, necrosis of a connective tissue involves an infectious or toxic element which provokes phagocytosis of the connective tissue fibers, the leukocytes being attracted by the infection. When infection is absent, the tissue may be destroyed without sequestration or without giving any external sign. She added that, in Regaud's cases, the bone had probably been killed by irradiation and the late necrosis was due to secondary infection.

Stark (1923) reported the case of a woman, aged forty-two years, who, in the course of one and a half years, had been exposed to five erythema doses of roentgen rays for excessive growth of hair around the mouth, each treatment being directed to four fields: each side of the chin, the upper lip, and the lower lip. The skin appeared to tolerate the exposures at the time, but one and a half years later necrosis of the middle portion of the alveolar process of the lower jaw occurred. Resection of a portion of the bone was followed by infection and a fistula. When the excised piece of bone was examined microscopically, evidence of necrosis could not be found. Blum (1924) mentioned a case of osteomyelitis of the mandible, somewhat similar to necrosis from phosphorus, which had been caused by some radio-active substance in paint used to render watch dials luminous.

Hoffman (1925) reported four fatal cases of necrosis of the mandible complicated by severe anemia and caused by radio-active substance introduced into the mouth by the brush used to apply so-called radium paint, composed of zinc sulphide, radium, and mesothorium, to the figures of watch dials. He also recorded eight other cases of similar necrosis, but only one with anemia. The patients, all of whom were still living, had been employed in the same factory. Sochoky (quoted by Hoffman) described the conditions of employment which had given rise to such lesions, which he justly attributed to the alpha rays and to the zinc sulphide collecting at one point on the mucosa and acting for a long time. Martland, Conlon, and Knef (1925) published an exhaustive report on the working conditions which gave rise to such disturbances. They also reported three cases. In one, the patient died with necrosis of the alveolar border of the mandible, ulceration and in-

fection of the soft tissues—including the soft palate—severe anemia, and toxemia. At necropsy, all the organs and bones tested with an electrometer were found to contain an appreciable quantity of radio-active matter. The second patient, who had progressive necrosis of the lower jaw and chronic, pernicious, leukopenic anemia, still lived. In the third patient slight necrosis of the jaw developed, but this healed. The expired air of the two last patients was found to contain a measurable quantity of radio-active substance.

Phemister (1926) reported four cases of sarcoma, in each of which from four to eight needles, each containing 12.5 mg. of radium, had been left in contact with bone in an aseptic field for from fifteen to twenty hours. Frequent roentgenograms were made during the ensuing twenty-two, forty-six, twenty-three, and two months, respectively. Distinct necrosis of bone was found, but the devitalized bone did not become detached as a sequestrum. In the second case, in which the course of events was watched over a period of forty-six months, the structural changes in the bone indicated replacement of the dead bone by new bone.

Ewing (1926) described three examples of radiation-osteitis. In one patient, a boy, aged sixteen years, a radium pack had been applied to the leg nine times in three months for endothelial myeloma of the tibia. Subsequently, radiodermatitis and recurring attacks of pain developed, and the leg was amputated one and a half years later. The bone was found to contain active tumor tissue, and the shaft was thickened at the expense of the marrow cavity. Microscopic inspection revealed viable tumor cells and zones of necrosis encased in dense fibrous tissue. The second patient had a giant-cell tumor of the distal end of the femur. After curettage of the growth a radium pack had been applied fifteen times; this led to necrosis of the skin and chronic osteitis which necessitated amputation. The third patient had an osteogenic sarcoma of the lower end of the femur, for which the part had been exposed to roentgen rays of short wave length eleven times in four months. Spontaneous fracture occurred later, and the extremity had to be amputated. The tumor was found largely destroyed, but the adjacent normal portion of the shaft was devitalized and callus was absent. Ewing thought the rays acted chiefly on the bone cells rather than on the lamellæ of the bones. Rahm (1927) described one case of necrosis of the body of the left half of the lower jaw resulting from irradiation following an operation for epithelioma of the lower lip. The patient had received four courses of treatment at intervals of one or two months; the rays had been made to converge toward the region through three separate fields. The patient had been given another course of irradiation six months later, and two additional courses within four months. Edema and induration of the chin appeared two years later, and, on further irradiation, the face swelled, a high fever developed, an abscess formed and broke, and a fistula communicating with bone persisted. A roentgenologic examination disclosed osteomyelitis, and a histologic examination showed inflammatory tissue.

Hueck and Spiess (1929) analyzed a series of seventy-six cases of tuberculosis of bones and joints in patients less than twenty years of age, who had been exposed to therapeutic irradiation. Fifteen did not show any noticeable disturbance of growth, but in sixty others definite inhibition of development was found. An apparent increase in growth was noted in only one case. The retardation in growth was attributed to the action of the tuberculous process on the epiphyses and to the inactivity of the patients and not to the roentgen rays.

St. George, Gettler, and Muller (1929) reported having exhumed, five years after her death, the body of a young woman, aged

Fig. 1. The right humerus March 23, 1924, showing tumor involving the upper third of the bone, with spontaneous fracture.

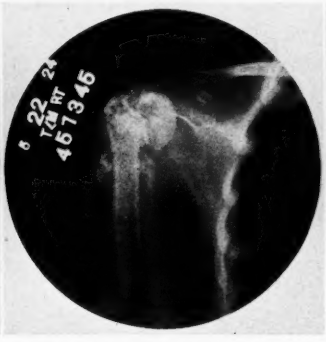

Fig. 2. The right humerus May 22, 1924, showing diminution in size of the tumor and increased density in the bone indicating repair.

Fig. 3. The right humerus in abducted position October 20, 1924, showing further reduction in the size of the tumor and more advanced repair of the bone.

twenty-five years, who had previously worked for four years as a painter of luminous watch dials. Necrosis was found in the inferior maxilla, part of which was absent, and, also, in the superior maxilla. All the organs and bones tested gave electroscopic and photographic evidence of radio-activity. They mentioned another case of supposed necrosis of bone, but the diagnosis rested only on clinical and roentgenologic data. Finally, Martland and Humphries (1929) mentioned that, in fifteen patients whose death was attributed to radium mesothorium poisoning incurred while they were employed in applying luminous paint to watch dials, radiation-osteitis, especially in the weight-bearing bones, was found, and in two osteogenic sarcoma had developed. The diagnosis in one case was based on the histologic appearance of the tumor found at necropsy, but in the other case only on clinical data.

I should like to supplement the foregoing evidence that sufficient doses of roentgen or radium rays may cause serious injury to bone by recording the following case.

A girl, aged nine years, registered at The Mayo Clinic, March 3, 1924, complaining of swelling of the right arm. In November, 1923, the child had injured the arm, which had swelled and become painful, but the parents had not paid any particular attention to this until December, when a roentgenologic examination of the right humerus had led to a diagnosis of tuberculosis or sarcoma. After the Holidays the swelling of the right arm had been stationary and the pain had disappeared, except when the upper portion of the arm had come in contact with other objects. The child had had a tendency to avoid using the extremity. Her previous history had been entirely negative. January 23, 1924, a specimen had been removed elsewhere, and the pathologist who examined the tissue had pronounced it small-cell sarcoma.

A general clinical examination and roentgenograms of the right humerus led to confirmation of the diagnosis of small-cell sarcoma of the upper third of the right humerus (Fig. 1). Moreover, microscopic examination of a section of the specimen previously removed revealed osteogenic sarcoma. Inspection of the roentgenograms showed that the tumor was complicated by spontaneous fracture of the bone. It was probably this fracture which had given rise to the swelling and pain which had caused the parents to have the child examined.

When the parents were told that the only

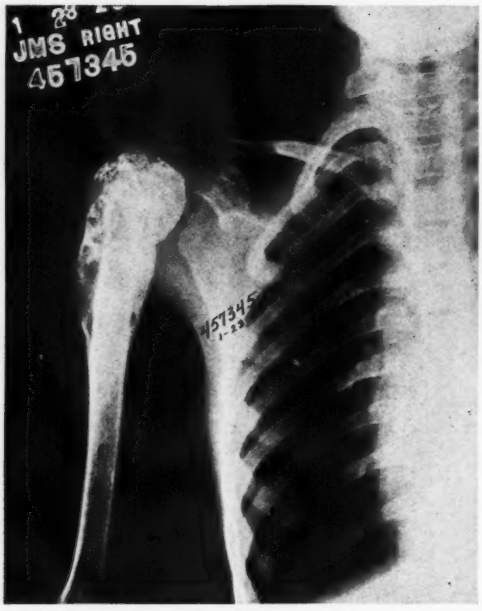

Fig. 4. The right humerus January 23, 1925, showing continued regression of the tumor and progressive repair of the bone.

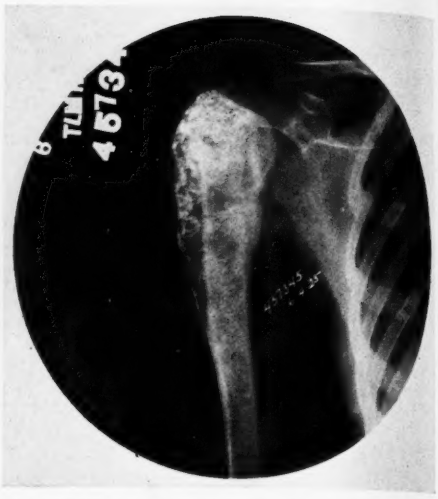

Fig. 5. The right humerus June 4, 1925, showing marked regression in the tumor and advanced repair of the bone.

treatment which gave any hope was either amputation of the right upper extremity at the shoulder or treatment by roentgen rays, they decided to try the latter. Before this was done, however, it was carefully explained to them that the treatment by roentgen rays would have to be thorough and systematic and that, in all probability, this would inhibit the growth of the irradiated bone and surrounding structures. On the parents' assurance that, in their anxiety to save the child's life, they were prepared to accept the risk, a course of roentgen-ray treatment was given between March 19 and 24, 1924, through seven separate fields. The beam of rays in each case was concentrated on the upper half of the right humerus and shoulder.

When the child returned, April 21, 1924, the skin over the upper part of the right arm and shoulder was faintly pigmented; otherwise, the child's condition was about the same as before. A second course of treatment with rays generated at moderate voltage was given between April 22 and 24; the distribution of such treatment was precisely the same as in the first instance. The child returned, May 21, in good general condition. All pain in the right arm had subsided, but the arm was still slightly larger than the left arm at the same level. A roentgenogram of the right humerus, made May 22, showed apparent improvement in the condition of the bone (Fig. 2). A third course of treatment with roentgen rays generated at moderate voltage was given May 22 and 23 through four fields only. The child was next seen July 21, 1924, when the parents reported that she tried to use the arm more than previously. Examination showed the tumefaction in the right arm to have diminished considerably. July 22 and 23, 1924, a fourth and last course of treatment with roentgen rays of short wave length was given. Following this the condition of the arm improved steadily and a roentgenogram, made October 20, 1924, showed considerable increase

in the density of the bone at the site of the tumor and reduction in the circumference of the arm at this level (Fig. 3). At the time it was uncertain whether such reduction in size was due to regression of the tumor or to atrophy from disuse. The child's weight increased normally and she used the right arm more and more freely. The next roentgenographic examination was made January 23, 1925 (Fig. 4). This disclosed continued regression of the tumor and further increase in the density of the bone. The child was still unable to raise the arm above the level of the shoulder. By June 4, 1925, the skin over the upper half of the right arm and right shoulder showed slight telangiectasis. The parents reported that, since her previous examination, the child had had six attacks characterized by severe headache, associated with nausea, vomiting, and sometimes fever. The fever had disappeared after the headaches had subsided. This gave rise to a suspicion of cerebral metastasis, but the presence of fever was puzzling because, in spite of careful investigation, it could not be clearly explained. A roentgenographic examination of the right humerus, June 4, 1925, showed a steady increase in the density of the bone, without evidence of malignant activity (Fig. 5).

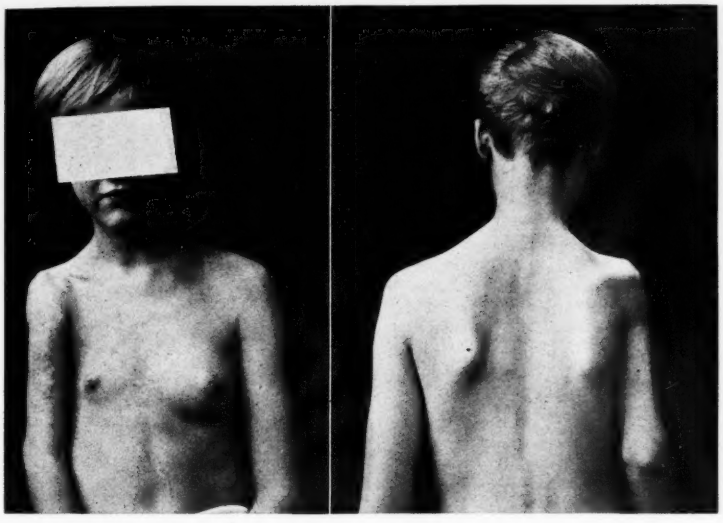

Fig. 6. Appearance of the child November 22, 1926, showing interference with the growth of the right arm and right shoulder, both as to bones and muscles, and also the telangiectasis of the skin.

When the child returned, February 25, 1926, the parents reported that the attacks of headache, which she had had previously, had not recurred since June, 1925. On examination, obvious asymmetry of the two shoulders and of the upper portion of the two upper extremities indicated inhibition of growth, not only in the right humerus, but also in the muscles around the right shoulder. Telangiectasis of the skin had increased. So far as the tumor in the humerus was concerned, no evidence of malignant activity, but rather clear evidence of continued repair, was found. In November, 1926, retardation of growth of the right arm and atrophy of the muscles around the right shoulder were still more

Fig. 7. The right humerus November 22, 1926, showing still greater regression of the tumor and more advanced repair of the bone, but such repair is not tending to restore the normal textural lines. This probably indicates that the reparative process has been modified by the action of the rays.

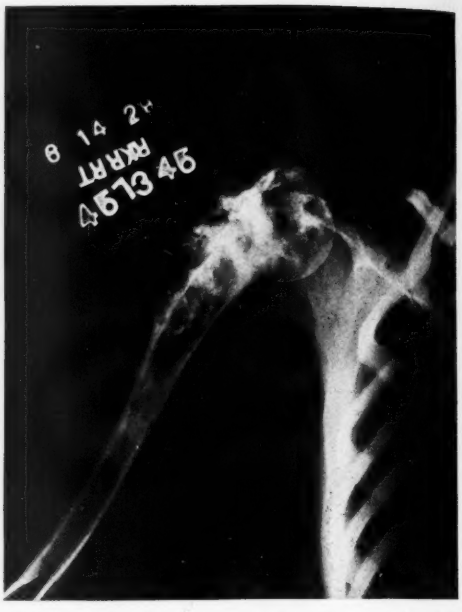

Fig. 8. The right humerus June 14, 1929, showing arrest of tumor and continued abnormal repair of the bone.

evident, as the corresponding parts on the opposite side had continued to grow at a normal rate (Fig. 6). The child was otherwise healthy and her mother said that she was becoming more and more active. The condition of the upper third of the right humerus had improved steadily, but a roentgenographic examination, November 22, 1926, made it clear that the reparative process in the bone was peculiar in that the deposition of new bone did not seem to be taking place in such a way as to give it a normal appearance. Even then it appeared probable that the reparative process had been modified by irradiation, which undoubtedly had destroyed many bone cells and thus led to abnormal repair (Fig. 7). When the child was seen again, in December, 1927, the condition of the right humerus was still improving and there was no evidence of malignant activity. The difference in growth between the right and left upper extremities and the muscular atrophy around the right shoulder were still greater. Up to this time the parents had been advised to prevent the child from using the right arm too much, but they were now advised to allow her to exercise the arm more freely.

Another examination in June, 1928, showed that the condition of the right humerus had continued to improve, and the child's mother reported that she had been active during the previous school year. The improvement in the condition of the right humerus and in the general health of the child continued steadily. She gradually increased her physical activities and even undertook swimming and tennis, in spite of the muscular atrophy. When she was examined, in June, 1929, her condition was satisfactory in every way (Fig. 8).

COMMENT

This case is interesting in that it shows clearly that irradiation of the rapidly grow-

ing bone of a nine-year-old child can retard its growth or permanently injure it according to the total dose of irradiation, but it also shows that the growth of the muscles and other structures irradiated may also be greatly impeded. Besides this, it is clear that while irradiation has caused the malignant tumor in the bone to retrogress, and although such retrogression appears to be complete, yet the reparative efforts of the bone have been modified considerably by irradiation.

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DISCUSSION

Dr. Francis Carter Wood (New York City): I can add cases that are similar to those recorded by Dr. Desjardins. For example, a boy of about eight years of age, who developed a Kaposi sarcoma on the forearm, was given heavy radiation. The boy, now about fourteen, is apparently well, but his left arm, the site of the radiation, is shrunken, the bones are shorter and smaller, and the muscles of the forearm are distinctly atrophied. I have assumed that the radiation of the epiphyses has checked the normal bone growth.

Dr. A. U. Desjardins (closing): I did not report this case with the idea of scaring any one from treating bone tumors—quite

the contrary; but it was important to bring to the attention of every one the possibility of retardation of growth and to make this better known than it now seems to be. Another point which I might mention in this connection is that many bone tumors, regardless of their character, are being treated in much the same way, and this also is a bad thing. The fact that growth can be retarded should make us more careful to this extent, that we should individualize varieties of bone tumors and give each variety a dose sufficient to deal with it without going too far. For instance, giant-cell tumors require only small doses of rays of medium wave length —it is easy to over-treat such a tumor and obtain inferior results; whereas, if it is not over-treated, excellent results may be obtained. With osteogenic tumors, on the other hand, we must take no chances and treat them with less regard for other factors. If the possibility of retarded growth is understood and the parents informed beforehand, they generally will accept the risk. They will usually accept such risk even if they are not told beforehand, but they may seriously object later if they have not been told.

TREATMENT OF MALIGNANT TUMORS OF THE EYE AND ORBIT BY RADIATION

By FREDERICK HASE RODENBAUGH, M.D., San Francisco

THE tissues of the eye and adnexa are of such variety in origin and structure that almost every known type of tumor has been found in these parts, either primary, through direct extension, or metastatic. In this survey are summarized those types which have been treated with radiotherapy, the results being compared with other methods of treatment as to conservation of normal tissue and permanency of cure. Obviously, many types of tumors have not received radiation therapy because of well-established surgical procedures, with favorable end-results, and in instances in which conservative methods are of little importance; for example, pigmented tumors of the choroid, with loss of vision from the tumor and rare local recurrence.

There are essential technical differences in the use of radiotherapy in malignant growths of the eye or orbit, as compared with other structures of the body in which these agents are in widespread use. The problem of dosage is most important. Radiotherapy, in the average case of neoplasm, is not conservative, and a maximum amount of fibrosis in the surrounding tissues is not harmful, but the reverse is true in lesions of the eye. Here a maximum conservation of normal tissue is essential. The lesions are, as a rule, well localized, and extreme conservation of the normal structures is of paramount importance.

The ophthalmologist and the radiologist have, of necessity, had a limited experience in these cases, with few opportunities to study the comparative effect of various combinations of radiotherapy with variable intensities and dosage, because of the comparative rarity of such lesions.

A general consideration of the physical factors in the treatment of this group would seem to indicate that there is a place for all variations of radiotherapy—the use of unfiltered radium or X-ray for superficial intense reactions and heavily filtered radium or X-ray for deep-seated lesions, the choice of agent being dependent on the extent and location of the lesion.

The agent of first choice, in our opinion, is radium, because of the ease of application and accuracy in measurement of dosage.

In corneal, scleral, and superficial lesions of the lids the technic, in general, is as follows: The use of from 25 to 50 mg. of unfiltered radium to produce an intense, superficial reaction, with a minimum depth dose. Such a technic assures a maximum conservation of normal tissue, and the applicators can be held in position and observed during treatment, two to ten minutes being the average dose.

In the more deep-seated growths, heavily filtered local or general orbital radiation is used and can be given with X-ray or radium. The choice of agent is not so important, but radium has been our personal preference for the smaller lesions.

The biological effects are apparently the same with X-ray or radium, the choice of agent depending on physical factors rather than biological. There is, however, some evidence to indicate that the end-results of some reported failures might have been improved with the use of divided doses to saturation, allowing sufficient time for regression before continuing treatment. With this technic the reaction is reduced to a minimum. The therapeutic response of similar neoplasms, so treated in other parts of the

body, is encouraging, and similar methods can be used to advantage on the structures in the orbit.

The control of radiation reactions of a neoplasm in the structures of the eye—cells undergoing involution from radiation—as pointed out by Poleff (1), can be observed by the ophthalmologist with instruments of precision, and offers a fertile field for investigation of the minute microscopic changes occurring in life. This is best demonstrated in the cornea by frequent observations of the changes in carcinoma cells following radiation treatment. No other structures permit this observation of human carcinoma cells *in vivo*, and such observations obviate the necessity for massive doses to large areas, when individual masses of cells may be treated as units.

The structures of the orbit for this survey may be roughly divided into three groups: (1) Epibulbar group, comprising the cornea, sclera, and ocular conjunctiva; (2) intra-ocular group; (3) the adnexa, including the lids, conjunctiva, and lacrimal glands.

EPIBULBAR TUMORS

In the first group (epibulbar tumors), the most common malignant tumor of the conjunctiva is the epithelioma, which most often takes its origin at the limbus. As elsewhere in the body, it is most common where types of epithelium change, or as part of a constitutional disease such as xeroderma pigmentosum. It is usually of a basal or mixed basal and squamous cell type, tending to slow erosion through the sclera, causing local destruction but seldom metastasizing. The growth, however, may occur on any part of the conjunctiva though rarely on the cornea, and tends to grow in the path of least resistance, outwards, assuming polypoid forms. The invasion of the sclera is, as a rule, late in the disease, and such tumors yield the most brilliant results to radiotherapy. They are ideally adapted to intense, sharply localized radium reactions with a minimum depth dose, as illustrated by Case No. 1, and should receive radiation as a primary therapeutic agent.

Case No. 1. Mr. M., age 62 years. Had enucleation of right eye many years previous to present examination, following injury. The duration of the lesion on the left eye is indefinite. The growth on the cornea had been present for several months, with gradual increase in size, until the patient consulted a physician because of irritation and inability to close the lids. Examination showed a papillomatous growth involving the outer half of the cornea, the center of the mass over the corneoscleral junction. The growth was irregular in shape, about 2 cm. in diameter and 1 cm. thick, the inferior border being thicker than the other portions of the tumor.

Treatment: Tumor divided into five areas to permit even distribution of radiation, the areas being determined by relative thickness of tumor.

Technic: Twenty-five mg. of radium sulphate in a glass tube, no filtration, held in place, the position of the tube observed during treatment. Exposure time: five to ten minutes to each area, varied as to the thickness of the tumor. This dose previously had been calculated by experiment for an intense superficial reaction. The entire field was covered at the first treatment (five areas); subsequent treatments in ten days. The progress of the treatment was observed under magnification and subsequent treatment was based on the appearance of cellular reaction. The clinical course showed a slight reaction from treatment, no ulceration; complete regression occurred in two months. Two years later, the patient was clinically well.

This case illustrates the relatively small amount of radium necessary to produce involution of carcinoma cells with a minimum amount of fibrosis in adjacent structures, a

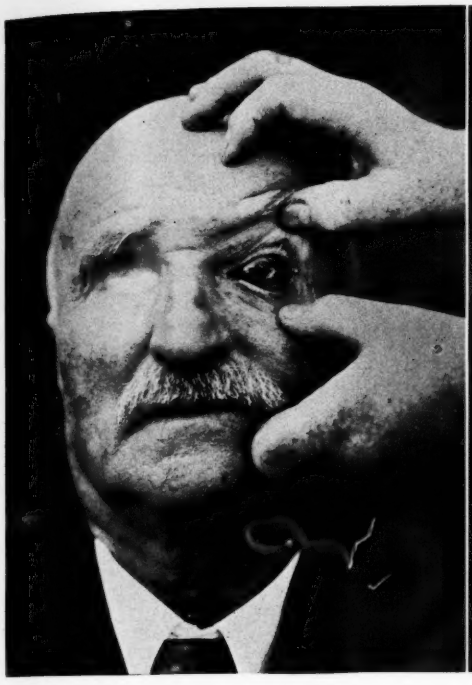

Fig. 1-*A*. Case No. 1. Carcinoma of conjunctiva at limbus; average type.

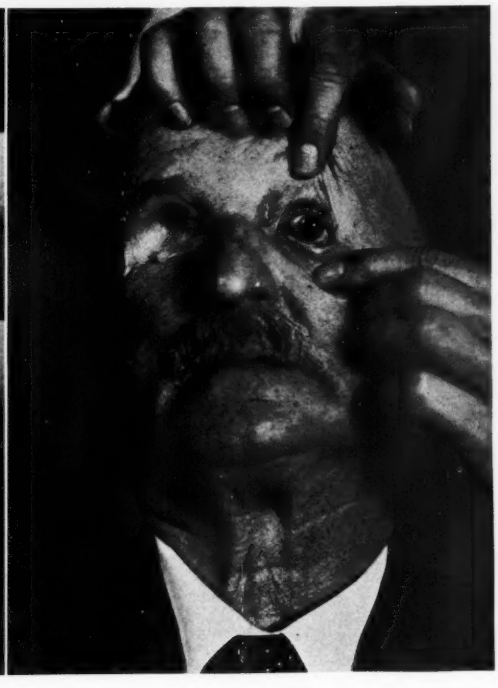

Fig. 1-*B*. Same case, showing results of intense unfiltered radium therapy in divided doses. Photograph taken two years after Figure 1-*A*.

most essential point in this case because of the previous accident to the right eye.

Sarcoma of the conjunctiva is uncommon and has no predilection for any special type. The pigmented form will be discussed later. In the cornea, sarcoma has been treated with successful results by the use of radium, analogous to the response of sarcoma to radiation therapy in other structures, and is illustrated by Case No. 2, using intense localized unfiltered radium with a minimum depth dose.

Case No. 2. D. G., Chinese, age 59 years. Duration of the lesion was approximately six months, though the patient was not definite as to the exact time of its appearance. He consulted an ophthalmologist when vision was impaired. The present examination shows a smooth, elevated, white neoplasm about 10 mm. in diameter and 5 mm. thick, on the inner half of the left cornea, with a superficial invasion of the cornea. The borders of the growth are smooth.

Diagnosis: Sarcoma.

Treatment: The lesion was divided into three areas, to permit of even distribution of the radiation, using 25 mg. of unfiltered radium, held in position during treatment. The center of the mass received nine minutes on the first treatment, eight subsequent treatments of five minutes each over various areas of the most active remaining portion of the tumor, the area to be treated being selected after observation under magnification.

Ten months later the lesion had entirely disappeared, without a scar. Four years later there had been no recurrence.

Fig. 2-*A*. Case No. 2. Sarcoma of cornea.

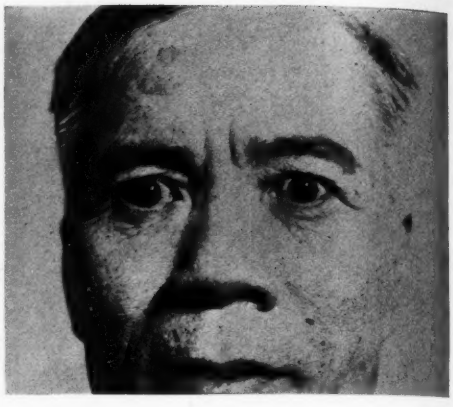

Fig. 2-*B*. Same case, showing results of intense unfiltered radium therapy in divided doses. Photograph taken two years after Figure 2-*A*.

Case No. 2 illustrates the results of divided dosage over a long period, with maximum conservation of tissue.

Melanosis oculi is a congenital condition, marked by focal or diffuse excessive pigmentation of choroid, iris, or conjunctiva, the ocular counterpart of the cutaneous nevus. Pigmented spots may also appear in the eyelids and over the skin of the face. Doherty (7) finds that 29 per cent of the cases eventually develop malignant melanoma.

In the conjunctiva, pigment spots appear at birth or later and may remain unchanged throughout life or become the source of malignant tumors. Parsons describes them as of epithelial origin, reproducing the picture of cutaneous pigmented moles. There are epithelial hyperplasias, shallow extensions into the deeper tissues, and the appearance of chromatophores. The lesions may gradually extend over the conjunctiva and eyelid, and, when incompletely removed, may be followed by the usual widespread dissemination through the blood vessels. Ewing has followed one congenital case for ten years, which gradually extended, was twice excised, and eventually became disseminated. Case No. 3 illustrates the type of response of the plaques of pigmented tumors on the conjunctiva and cornea to radium, with intense unfiltered radium therapy, followed by regression of the growths.

Case No. 3. H., age 64 years. The past history reveals that thirty years ago the patient first noticed pigmentation in the right eye, probably on the conjunctiva. For the past fifteen years he has noticed steady increase in the pigmentation of the scleral conjunctiva, until two years ago when a marked increase took place, with invasion of the cornea and formation of the nevi of the conjunctiva on both lids.

Examination showed multiple nevi on both lids, with patchy pigmentation of the ocular conjunctiva. There was an irregular, superficial infiltration of the upper layers of the cornea on the superior border, the growth being smooth and slightly elevated, with considerable pigmentation. Surgical removal and histological examination of the larger nevi of the lids showed melanotic sarcoma.

Unfiltered radium treatment was used on the superficial flat pigmented plaques on the lids, with prompt involution of the growth. Eleven areas of pigmentation on the lids and conjunctiva were treated over a period of

three years. At the present time there is a small area of pigmentation on the scleral conjunctiva which has developed recently.

The most interesting phase of this case—the conjunctival growths and the corneal infiltration—responded to one treatment of unfiltered radium, with complete regression of the infiltration in three months and restoration of vision. There were a few recurrences, but in this instance they responded quickly to treatment. Conservation of vision was most important to this patient, as there is marked impairment of vision in the other eye.

This case further illustrates the prompt response to an intense radium reaction locally applied to the tumor, with minimum damage to the normal cells. However, such cases should be kept under observation and the recurrences promptly treated.

Other varieties of malignant tumors comprise angiofibroma, hemangioma, lymphoma, and lymphangioma, and are susceptible to treatment by radiation therapy with proper technic, the results being comparable to the response to treatment of similar lesions in other structures.

Of the benign and borderline types, the fibroma, papilloma, granuloma, and nevus, owing to their histological structure, have been treated with radiation therapy with success, the technic and dosage depending on the size and location of the growth. Case No. 4 illustrates results of radium therapy in a severe type of granuloma.

Case No. 4. B. L., age 6 years. Multiple granulomas of the conjunctiva. Three previous operations for removal have been followed by prompt recurrence. The present examination shows multiple large pedunculated masses at the outer and the inner canthus of the left eye. *Treatment:* Twenty-five mg. unfiltered radium, held in position at the base of granuloma for four minutes. No recurrence of growths three years later.

INTRA-OCULAR TUMORS

In the second group (intra-ocular tumors), the most frequent and malignant are the melanomas or melanosarcomas, which have a variety of histological forms but a uniformly high degree of malignancy. They occur in the choroid, iris, and ciliary body. The response of this group to radiation has varied. In general, they have been most resistant, and the number of cases of primary lesions receiving treatment has been limited. The high percentage of primary cures following surgical removal (60–80 per cent), and the infrequent local recurrence, in most instances has precluded the use of radiation therapy. Conservative treatments are of only relative importance, as these growths have usually already destroyed vision when seen by the radiologist.

There are, however, cases of local tumors of the iris and ciliary body that, clinically, resemble the non-pigmented form of sarcoma. These have responded to radiation without recurrence of the lesion. One such case has been observed by the writer after a five-year period, but the diagnosis is, of course, questionable, because histological studies are not possible when conservative treatment is used.

Two similar pigmented lesions of the iris have shown no response to radiation therapy in average doses. Large doses are not indicated, as there is definite evidence to show that massive radiation produces permanent changes in the lens, and such changes would not increase the functional results as compared with surgical methods.

Glioma of the retina is a rare type of specific tumor growth and is favorably influenced by radiation, but the regression is usually only temporary.

A summary of the effects of radiation on intra-ocular tumors leaves much to be desired, but the disappearance of tumors of the iris and ciliary body, of doubtful nature, should indicate that such tumors be radiated

before resorting to more radical methods of treatment.

GROUP III

In Group III, the primary tumors of the orbit are numerous. Cysts are common—sebaceous, dermoid, mucocele, meningocele—and none of this group is amenable to radiation therapy. Teratoma occasionally occurs, but there are no records of successful treatment.

The angioma, particularly cavernous angioma, fibroma, myxoma, and sarcoma occur and are influenced by radiation therapy, the response varying with the histological structure.

Of the metastatic tumors, many types are found late in malignant disease, and can be arrested in their local growth in the same ratio as the primary tumors are susceptible to radiation. In orbital tumors from direct extension from the eyeball, adjacent bones, and the nasal cavity, as well as from subdural endotheliomas, meningeal sarcomas, and carcinomas of the pituitary region of the cranial cavity, the same grouping or response to radiation is observed.

Standard text-books and numerous authors describe and illustrate the effects of radiation on such frequent tumors as lymphoma and sarcoma, and the favorable results of radiation treatment are too well known to need repetition.

Tumors of the lacrimal glands occur in many forms: the lymphoid hyperplasia seen in leukemia and the chronic inflammatory types are difficult to differentiate, but respond to radiation therapy. The most common type of primary tumor is a mixed tumor similar to the mixed tumors of the parotid, its response to radiation depending on the character of the cells.

Tumors of the lid, of the benign type, are numerous: hyperkeratosis, angioma, and xanthoma are common and susceptible to radiation therapy, with excellent results.

Of the malignant tumors of the lid, adenocarcinoma of the lids occurs rarely; sarcoma of various types frequently, and they are susceptible to radiation. Their response is dependent on their histological characteristics. The most common type of malignant tumor is the epithelioma, the basal and squamous types appearing in equal number. The squamous-cell type is most malignant and least susceptible to radiation. The effects of radiation in the basal-cell type are most satisfactory and results are too well known to require further consideration. Primary radiation treatment is the first choice in such cases.

A brief outline of the present status of the effects of radiation in tumors of the orbit may be summarized as follows:

(1) In tumors of the conjunctiva and cornea, radiation, preferably from radium, with a maximum conservation of normal tissue looking to clinical cure should be given first consideration.

(2) In basal-cell epitheliomas of the adnexa, as elsewhere in the body, the clinical cures are satisfactory and radiation is superior to other methods of treatment.

(3) The angiomas, lymphomas, sarcomas, granulomas, fibromas, and nevi, occurring as primary tumors, are susceptible to radiation, their response varying with their histological structure.

(4) The numerous metastatic tumors will vary in their response to radiation, their susceptibility depending on their histological structure.

(5) Types of localized tumors of the iris or ciliary body, of doubtful nature, have been favorably influenced by radiation, and such treatment should receive consideration before resorting to radical surgical methods. It is of greater importance to secure clinical regression of a newgrowth, with conservation of essential structures, than to have a histological study, with loss of function.

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